# UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE FARMACIA

Departamento de Química Orgánica y Farmacéutica


## TESIS DOCTORAL

# Sinthesis of nitrogen heterocycles via new β-enaminone-initiated multicomponent reactions

# Síntesis de heterociclos nitrogenados a través de nuevas reacciones multicomponente iniciadas por la formación de una β-enaminona

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

**Padmakar Apparao Suryavanshi**

Directores

José Carlos Menéndez Ramos
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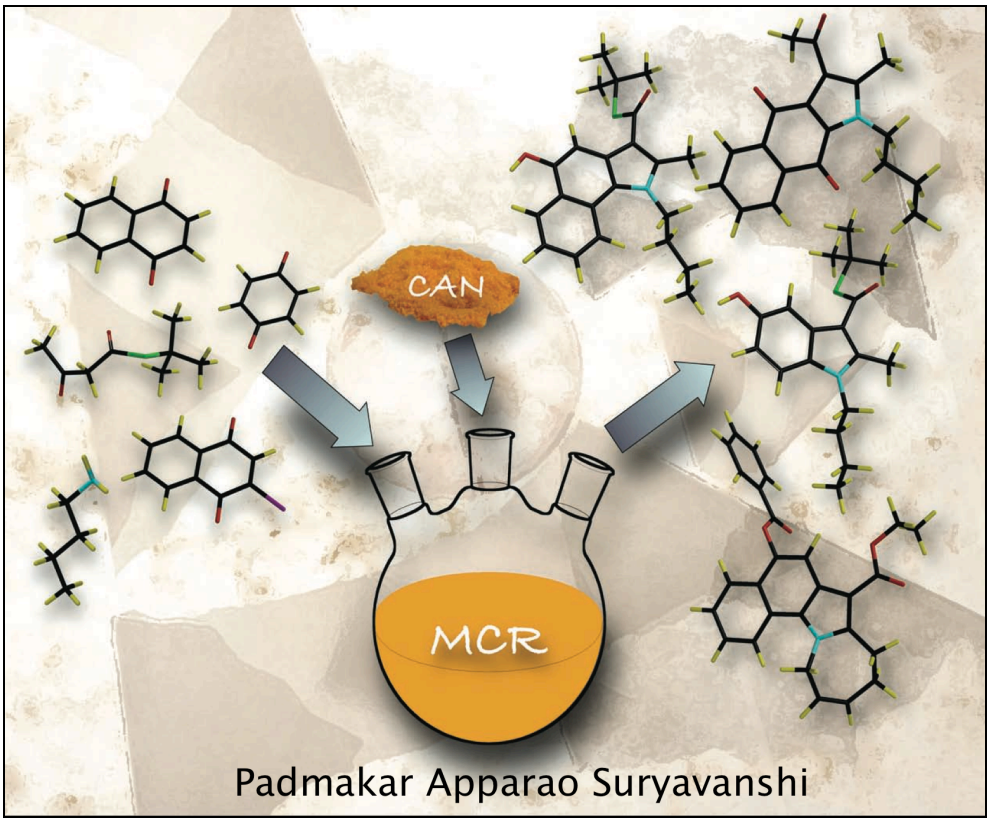
**Madrid, 2014**

Universidad Complutense, Madrid

# SYNTHESIS OF NITROGEN HETEROCYCLES *VIA* NEW β-ENAMINONE-INITIATED MULTICOMPONENT REACTIONS

Doctoral thesis




Padmakar Apparao Suryavanshi

Supervisors: José Carlos Menéndez, Vellaisamy Sridharan

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DEPARTAMENTO DE QUÍMICA ORGÁNICA Y FARMACÉUTICA


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DOCTORAL THESIS

PADMAKAR APPARAO SURYAVANSHI

Supervisors: José Carlos Menéndez Ramos
Vellaisamy Sridharan

Madrid, November 2013

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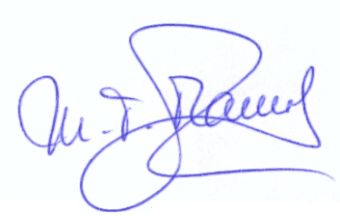
CERTIFICA:

Que el trabajo contenido en la memoria adjunta, titulada:

"**Synthesis of nitrogen heterocycles *via* new β-enaminone-initiated multicomponent reactions**"

que presenta **D. Padmakar Apparao Suryavanshi** como tesis doctoral, ha sido realizado en los laboratorios de este Departamento bajo la dirección de los Dres. José Carlos Menéndez Ramos, Profesor Titular de este Departamento, y Vellaisamy Sridharan, inicialmente investigador postdoctoral en este Departamento y en la actualidad profesor de la Universidad SASTRA, en Thanjavur (Tamilnadu, India).

Y para que conste donde proceda, expido y firmo el presente certificado en Madrid, a 4 de Noviembre de dos mil trece.



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CERTIFICAN:

Que el trabajo contenido en la memoria adjunta, titulada:

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que presenta **D. Padmakar Apparao Suryavanshi** como tesis doctoral, ha sido realizado en los laboratorios de este Departamento bajo su dirección y que cumple los requisitos para un trabajo de esta índole, por lo que autorizan su presentación.

En Madrid, a 4 de Noviembre de 2013

Fdo. J. Carlos Menéndez Ramos

Fdo. Vellaisamy Sridharan

**To My Family & Friends**

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Finally a huge thanks to my family, my mother Kalavanti A. Suryavanshi and my father Apparao E. Suryavanshi, for their moral support, unconditional love and patience over the years. I also deeply thank my brother Ganesh and my sister-in-law Gouri, and also my sister Vijaya, my brother-in-law Vishnu and my cute niece Akshara. A great deal of thanks has to go to my all extended family.

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And thanks to the utmost God, the supreme Guide for this beautiful life!

Padmakar A. Suryavanshi

## TABLE OF CONTENTS

## ABBREVIATIONS

| | |
|---|---|
| Ac | Acetyl |
| AcOH | Acetic acid |
| Ar | Aryl |
| Bn | Benzyl |
| Br | Bromide |
| br s | Broad singlet |
| Bu | Butyl |
| *t*-Bu | *tert*-Butyl |
| Bz | Benzoyl |
| Calcd. | Calculated |
| Cat. | Catalytic/Catalyst |
| CAN | Ceric ammonium nitrate |
| Conc. | Concentrated |
| d | Doublet |
| DCM | Dichloromethane |
| dd | Doublet of doublet |
| DEPT | Distortionless Enhancement by Polarization |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| equiv. | Equivalent |
| Fig. | Figure |
| g | Gram |
| h | Hour |
| IR | Infrared |
| LDA | Lithium diisopropylamide |
| Lit. | Literature |
| m | Multiplet |
| Me | Methyl |
| MeCN | Acetonitrile |
| MeI | Methyl iodide |
| MeOH | Methanol |
| mL | Mililiter |

| | |
|---|---|
| mmol | Millimole |
| min | Minutes |
| MP | Melting point |
| MHz | Megahertz |
| NMR | Nuclear magnetic Resonance |
| *n*-Pr | *n*-Propyl |
| Ph | Phenyl |
| Pyr | Pyridine |
| ppm | Parts per million |
| rt | Room temperature |
| s | Singlet |
| t | Triplet |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TLC | Thin Layer Chromatography |

**LIST OF PUBLICATIONS**

The work carried out during my doctoral studies has led so far to the following publications (see also Appendix 3):

1. **Padmakar A. Suryavanshi**, Vellaisamy Sridharan and J. Carlos Menéndez, 'Expedient, one-pot preparation of fused indoles *via* CAN-catalyzed three-component domino sequences and their transformation into polyheterocyclic compounds containing pyrrolo[1,2-*a*]azepine fragments'.
   *Organic and Biomolecular Chemistry* **2010**, *8*, 3426–3436.
   Inside front cover of the *Organic and Biomolecular Chemistry* issue **2010**, *8* (15).

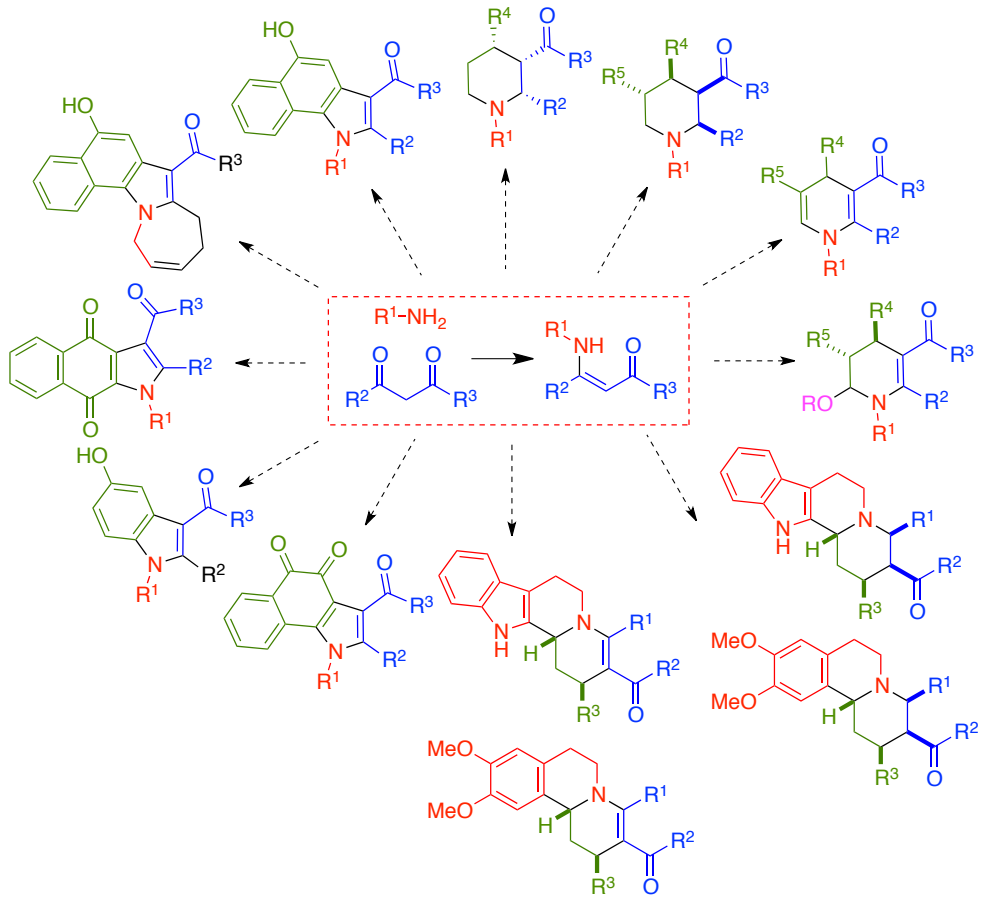
2. **Padmakar A. Suryavanshi**, Vellaisamy Sridharan and J. Carlos Menéndez, 'A new CAN-catalyzed domino process related to the Nenitzescu reaction: Very concise access to fused *ortho*-indolequinones from simple precursors'.
   *Tetrahedron*, **2013**, *69*, 5401-5406.
   Front cover of the *Tetrahedron* issue **2013**, *69* (26).

3. **Padmakar A. Suryavanshi**, Vellaisamy Sridharan and J. Carlos Menéndez, 'A CAN-catalyzed, enaminone-initiated multicomponent domino reaction for the synthesis of indoloquinolizidines and benzoquinolizidines from acyclic precursors'.
   *Chemistry: A European Journal* **2013**, *19*, 1320-13215.

4. **Padmakar A. Suryavanshi**, Vellaisamy Sridharan and J. Carlos Menéndez, 'Diastereoselective synthesis of polysubstituted, functionalized piperidines based on a CAN-catalyzed multicomponent reaction'.
   Manuscript in preparation

5. Vellaisamy Sridharan, **Padmakar A. Suryavanshi** and J. Carlos Menéndez, 'Advances in the Chemistry of Tetrahydroquinolines'. *Chemical Reviews* **2011**, *111*, 7157-7259.

**GRAPHICAL ABSTRACT**



# English summary / Resumen en inglés

## 1. Introduction

Multicomponent reactions can be defined as convergent reactions where three or more reagents are combined in such a way that the final product retains significant portions of all starting materials. Multicomponent reactions have recently experienced an explosive growth prompted by their key role in pharmaceutical research, especially in the fields of combinatorial and diversity-oriented synthesis, since they are perfectly suited for the creation of libraries with a high degree of structural diversity. As a consequence, the development of new multicomponent reactions is a significant part of the research work currently carried out in pharmaceutical companies.

The best-studied multicomponent reactions are those involving the use of isonitriles as one of the components, the so-called IMCRs (*isocyanide-based multicomponent reactions*). Most IMCRs are focused on the construction of peptide-like structures and can be referred to two classical reactions described by Paserini and Ugi. Bearing in mind that more than 60% of drug molecules are heterocycles, it is surprising that multicomponent reactions leading directly to heterocyclic frameworks have not received closer attention. In this context, the present thesis deals with the application of multicomponent strategies to the synthesis of functionalized polyheterocyclic frameworks, using reaction sequences that start with the formation of a β-enaminone. These are are important intermediates in synthesis, but their involvement as intermediates in multicomponent reactions has been relatively little studied.

## 2. Objectives

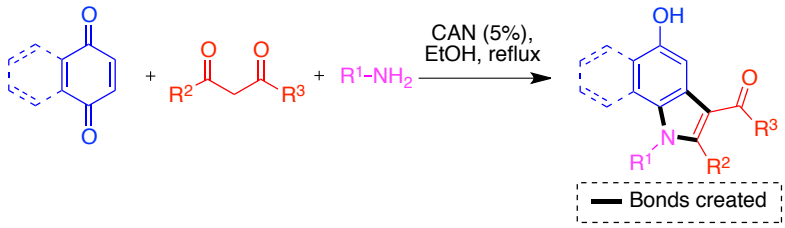
In the context of the development of multicomponent reactions initiated by the formation of a β-enaminone for the synthesis of heterocycles with potential pharmacological interest, the present thesis has the following specific objectives:

1. Development of a multicomponent, general version of the Nenitzescu indole synthesis.
2. Use of the Nenitzescu products as starting materials for complexity-generating reactions as an application of the build-couple-pair approach to the generation of molecular diversity.
3. Development of a variation of the Nenitzescu reaction that allows the synthesis of indolequinones by adding a leaving group to the quinone starting material.
4. Development of a three-component method for the synthesis of β-enaminones coupled to naphthoquinone and their transformation into *ortho*-quinones derived from the benzo[*g*]indole system.
5. Development of a one-pot synthesis of areno[*a*]quinolizines based on the combination of a multicomponent synthesis of 6-ethoxy-1,4,5,6-tetrahydropyridines previously developed by our group (see Scheme 1.13) with the Pictet-Spengler reaction.
6. Application of the above-mentioned multicomponent synthesis of 6-ethoxy-1,4,5,6-tetrahydropyridines to the preparation of polysubstituted piperidine derivatives, either directly or *via* its previous adaptation to the preparation of 1,4-dihydropyridines.

## 3. Results and discussion

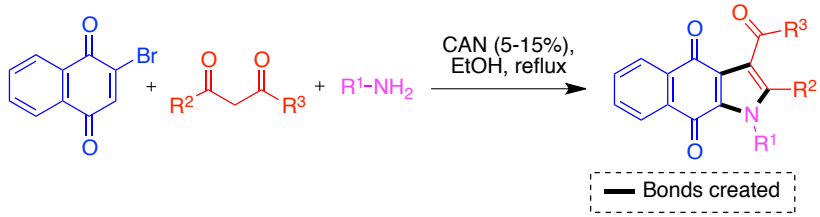
The main results obtained are summarized below in graphical form.

First objective: Multicomponent Nenitzescu indole synthesis using CAN as a Lewis acid.

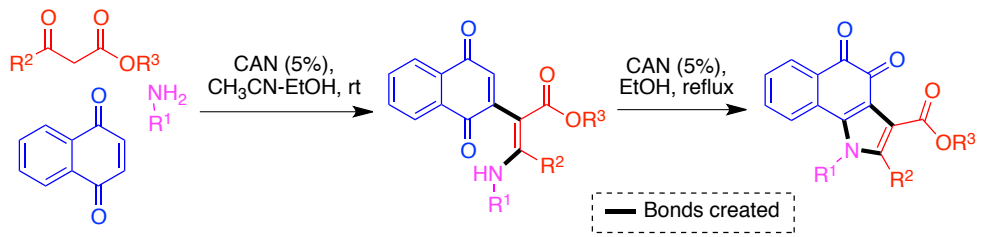



Second objective: Complexity-generating reactions from the Nenitzescu products.

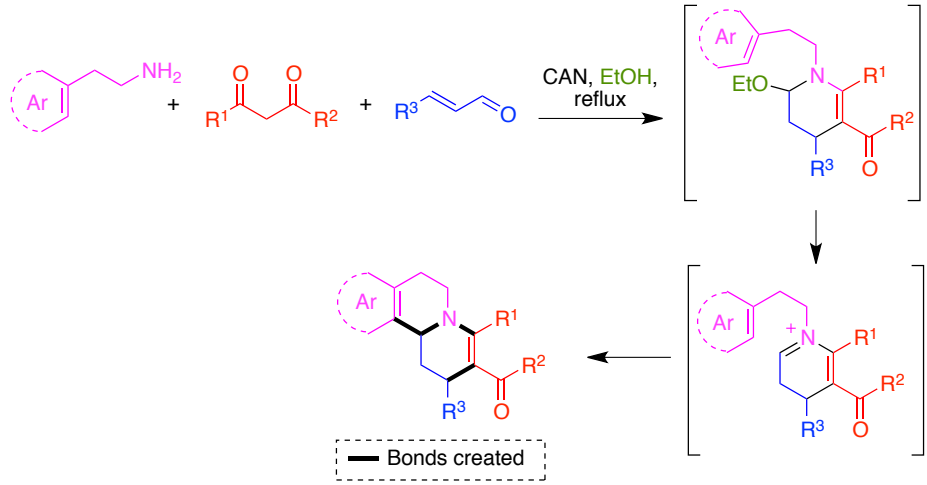

Third objective: Synthesis of linear indolequinones *via* a variation of the Nenitzescu reaction.



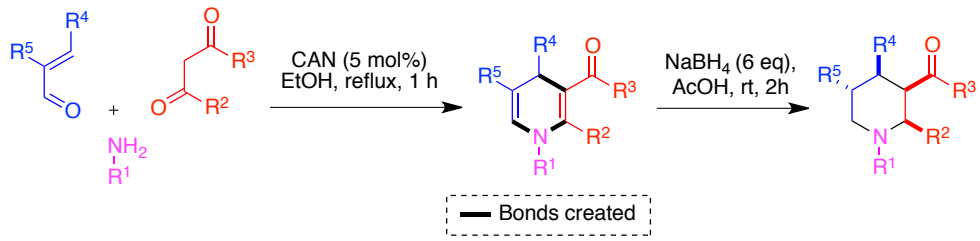

Fourth objective: Three-component synthesis of benzo[*g*]indoles containing an *ortho*-quinone structural fragment.



Fifth objective: Multicomponent synthesis of areno[*a*]quinolizines




Sixth objective: Synthesis of polysubstituted piperidine derivatives based on a multicomponent reaction.




## 4. Conclusions

1. The reaction between naphthoquinone, β-dicarbonyl compounds and primary amines in refluxing ethanol containing Ce(IV) ammonium nitrate (CAN) as a Lewis acid catalyst affords 5-hydroxybenzo[*g*]indole derivatives, in a three-component version of the Nenitzescu indole synthesis. A similar reaction starting from benzoquinone affords 5-hydroxyindoles. These Lewis acid-catalyzed multicomponent Nenitzescu reactions appear to take place by a mechanism different from the standard one.

2. Suitably substituted Nenitzescu products are adequate starting materials for ring-closing metathesis reactions as complexity-generating events that allow the generation of molecular diversity by application of the build-couple-pair approach.

3. The replacement of the naphthoquinone component in the Nenitzescu reaction by 2-bromonaphthoquinone leads to the deviation of the course of the reaction towards a Michael-Michael domino process that affords linear benzo[*f*]indolequinones.

4. A slight modification in the conditions of the reaction between naphthoquinone, β-dicarbonyl compounds and primary amines consisting of the use of room temperature conditions in ethanol-acetonitrile allows the preparation of β-enaminones bearing a quinone substituent at their α position. These compounds are suitable starting materials for the preparation of tricyclic *ortho*-quinone derivatives derived from the benzo[*g*]indole system.

5. The combination of a multicomponent synthesis of 6-ethoxy-1,4,5,6-tetrahydropyridines previously developed by our group with the Pictet-Spengler reaction allowed the development of a one-pot synthesis of areno[*a*]quinolizines from arylethylamines, β-dicarbonyl compounds and α,β-unsaturated aldehydes in refluxing ethanol *via* the generation of two rings, two C-C bonds and two C-N bonds in a single synthetic operation.

6. Dihydropyridines were readily available from primary amines, β-dicarbonyl compounds and α,β-unsaturated aldehydes *via* a modification of the above-mentioned multicomponent reaction. Their reduction with sodium triacetoxyborohydride (STAB) allowed the preparation of polysubstituted piperidine derivatives with complete diastereoselection. 6-

Ethoxy-1,4,5,6-tetrahydropyridines could be reduced by the same method, affording identical results.

# Resumen en español

**Spanish summary**

## 1. INTRODUCCIÓN

Las exigencias actuales para un nuevo método de síntesis orgánica van más allá de las tradicionales de quimio-, regio- y estereoselectividad, y pueden resumirse en los siguientes aspectos:

1. Creación de una elevada diversidad y complejidad molecular.[1]
2. Empleo de materiales de partida sencillos y asequibles.
3. Simplicidad experimental, que conduce a la posibilidad de automatización.
4. Bajo impacto medioambiental (uso de disolventes poco contaminantes, economía atómica, bajo consumo de energía, etc.).

De los requisitos anteriores, el primero puede considerarse de una especial importancia ya que la longitud de una ruta de síntesis depende de la complejidad molecular generada mediante cada operación sintética. Ésta, a su vez, está relacionada con el número de enlaces creados por operación.

1 Algunas revisiones sobre síntesis orgánica orientada a la generación de diversidad molecular y sus implicaciones en la búsqueda de compuestos bioactivos: (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Spring, D. R. *Org. Biomol. Chem*. **2003**, *1*, 3867. (c) Burke, M. D.; Berger, E. M.; Schreiber, M. L. *Science* **2003**, *302*, 5645. (d) Burke, M. D., Schreiber, S. L. *Angew. Chem. Int. Ed*. **2004**, *43*, 46. (e) Tan, D. S. *Nature Chem. Biol*. **2005**, *1*, 74. (f) Wessjohann, L. A.; Ruijter, E. *Top. Curr. Chem*. **2005**, *243*, 137. (g) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem*., **2008**, *6*, 1149.

Por tanto, el desarrollo de procesos que permitan la creación de varios enlaces en una sola operación se ha convertido en uno de los mayores y más atractivos retos de la síntesis orgánica.[2] Entre las metodologías más prometedoras en este sentido puede destacarse el desarrollo de reacciones dominó y multicomponente, cuyo estudio puede considerarse como uno de los pilares para el desarrollo futuro de la síntesis orgánica.

Las reacciones multicomponente pueden definirse como procesos convergentes en los que se combinan tres o más reactivos en una única operación sintética de modo que el producto final contiene fragmentos significativos de todos los componentes.[3,4,5] La reacción multicomponente

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2 (a) Revisión de las reacciones genaradoras de varios enlaces: Coquerel, Y.; Boddaert, T.; Presset, M.; Mailhol D.; Rodriguez, J.; *Ideas in Chemistry and Molecular Sciences,* en *Advances in synthetic chemistry*, ed. B. Pignataro, Wiley-VCH, Weinheim, vol. 1, capítulo 9, **2010**. (b) Ver también el siguiente número especial: Menéndez, J. C. (ed.), *Curr. Org. Chem*. **2013**, *17*, número 18. Multibond forming reactions. A new frontier in the synthesis of heterocycles.

3 Libro monográfico sobre reacciones multicomponente: (a) Zhu, J.; Bienaymé, H. (eds.), Multicomponent Reactions. Wiley-VCH, 2005.

4 Algunas revisiones generales sobre reacciones multicomponente, con especial énfasis en el uso de isonitrilos en los casos (a-c y g): (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3168. (b) Ugi, A. *Pure Appl. Chem.* **2001**, *73*, 187. (c) Ugi, A. *Molecules* **2003**, *8*, 53. (d) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (e) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (f) Tejedor, D.; González-Cruz, D.; Santos-Expósito, A.; Marrero-Tellado, J. J.; de Armas, P.; García-Tellado, F. *Chem. Eur. J.* **2005**, *11*, 3502. (g) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (h) Liéby-Muller, F.; Simon, C.; Constantieux, T.; Rodriguez, J. *QSAR Comb. Sci.* **2006**, *25*, 432. (i) Guo, H.; Ma, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 354 (k) Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484. (j) Touré, B. B.; Hall, D. G. *Chem. Rev*. **2009**, *109*, 4439. (k) Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300. (l) Eckert, H.; *Molecules* **2012**, *17*, 1074. (m) Singh, M.S.; Chowdhury, S. *RSC Adv*. **2012**, *2*, 4547.

5 Revisiones sobre reacciones multicomponente asimétricas: (a) Ramón, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602. (b) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. (c) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. *Tetrahedron: Asymmetry* **2010**, *21*, 1085. (d) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. en *Targets in Heterocyclic Systems - Chemistry and Properties*, Vol. 15, Eds.: Attanasi, O. A.; Spinelli, D. Societá Chimica Italiana, Roma, **2011**, p. 140. (e) Yu, J.; Shit, F.; Gong, L. Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (f) de Graaff, C.; Ruijter E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969.

ideal es la que permite la adición simultánea o casi simultánea de todos los materiales de partida y catalizadores, y requiere que todos ellos se combinen de una manera ordenada y bajo las mismas condiciones de reacción para dar lugar a los productos finales. Sin embargo, para evitar reacciones secundarias, es necesario en muchos casos adicionar los reactivos de forma consecutiva, hablándose entonces de reacciones multicomponente secuenciales.

El campo de las reacciones multicomponente tiene una larga historia y de hecho algunas de ellas, como las clásicas reacciones de Strecker, Biginelli o Hantzsch, se descubrieron durante la segunda mitad del siglo XIX (esquema 1.3). Sin embargo, el enorme interés que existe actualmente en el desarrollo de nuevas reacciones multicomponente data de la década de 1990. Este resurgimiento se debió fundamentalmente al desarrollo por la industria farmacéutica de métodos de ensayo biológico de alto rendimiento (*high-throughput screening*), lo que planteó a los químicos de síntesis el reto de preparar de forma rápida grandes colecciones de moléculas, o quimiotecas.[6]

Las reacciones multicomponente más estudiadas hasta la fecha son las que utilizan isonitrilos como uno de los materiales de partida (IMCRs, *isocyanide-based multicomponent reactions*),[4a-c,g] que están orientadas normalmente a la preparación de estructuras de tipo peptídico. La mayor parte de los procesos multicomponente de este tipo se basan en dos reacciones clásicas descritas por primera vez por Paserini y Ugi.

6 Aplicaciones de las reacciones multicomponente en el descubrimiento de fármacos: (a) Hann, M. M.; Leach, A. R. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 856. (b) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304. (c) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085. (d) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (e) Ulaczyk-Lesanko, A.; Hall, D. G. *Curr. Opin. Chem. Biol.* **2005**, *9*, 266. (f) Slobbe, P.; Ruijter E.; Orru, R. V. A. *Med. Chem. Commun*. **2012**, *3*, 1189. (g) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev*. **2012**, *112*, 3083. (h) Ruijter E.; Orru, R. V. A. *Drug Discov. Today: Technol.* **2013**, *10*, 15-20.

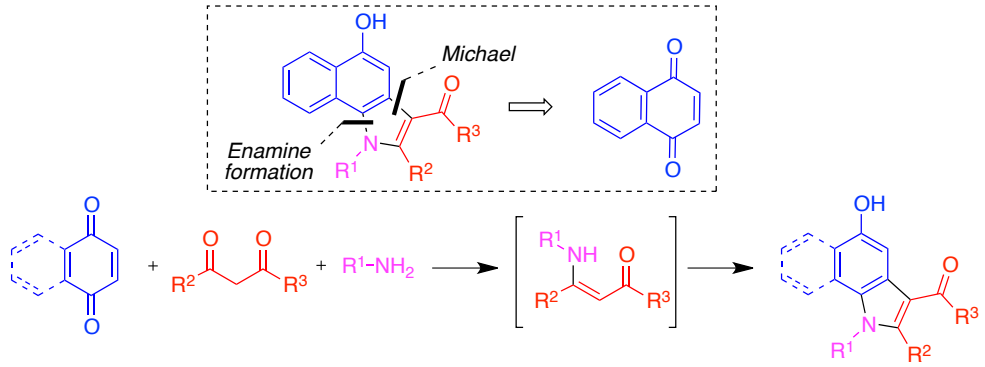
Por otra parte, teniendo en cuenta que más del 60% de los fármacos son heterociclos, resulta sorprendente que no se haya prestado una mayor atención al desarrollo de reacciones multicomponente que conduzcan directamente a esqueletos heterocíclicos.[7] De hecho, puede afirmarse que la creación de diversidad molecular en el campo de los heterociclos mediante el empleo de reacciones multicomponente está relativamente poco desarrollada y, sobre todo, que son escasos los ejemplos bibliográficos de síntesis de dianas poliheterocíclicas basada en este tipo de metodología.

7 Revisiones representativas: (a) Sapi, J.; Laronze, J.-Y. *Arkivoc* **2004** (vii) 208. (b) D'Souza, D. M.; Mueller, T. J. J. *Chem. Soc. Rev*. **2007**, *36*, 1095. (c) Isambert, N.; Lavilla, R. *Chem. Eur. J.* **2008**, *14*, 8444. (d) Sunderhaus, J. D.; Martin, S.-F. *Chem. Eur. J*. **2009**, *15*, 1300. (e) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. *Chem. Asian J.* **2010**, *5*, 2318. Monografía: Ruijter, E.;. Orru, R. V. A. *Synthesis of heterocycles via multicomponent reactions,* vols. 1 y 2*,* Springer Verlag, **2010** (*Topics in Heterocyclic Chemistry*, volúmenes 23 y 25).

## 2. OBJETIVOS

Las β-enaminonas son intermedios importantes en síntesis orgánica,[8] pero su participación en reacciones multicomponente ha sido relativamente poco estudiada. El objetivo general de la presente tesis doctoral es contribuir al escubrimiento y estudio de nuevas reacciones multicomponente para la síntesis de heterociclos complejos, iniciadas por la formación de una β-enaminona. Este objetivo general se ha concretado en el estudio de los siguientes puntos:

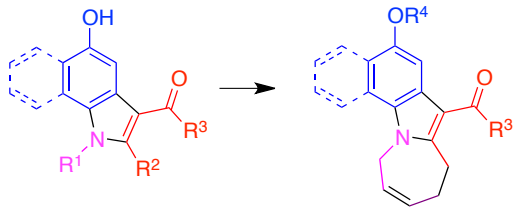
1.- Desarrollo de una versión generalizada y multicomponente de la síntesis de indoles de Nenitzescu (esquema 1).




**Esquema 1**

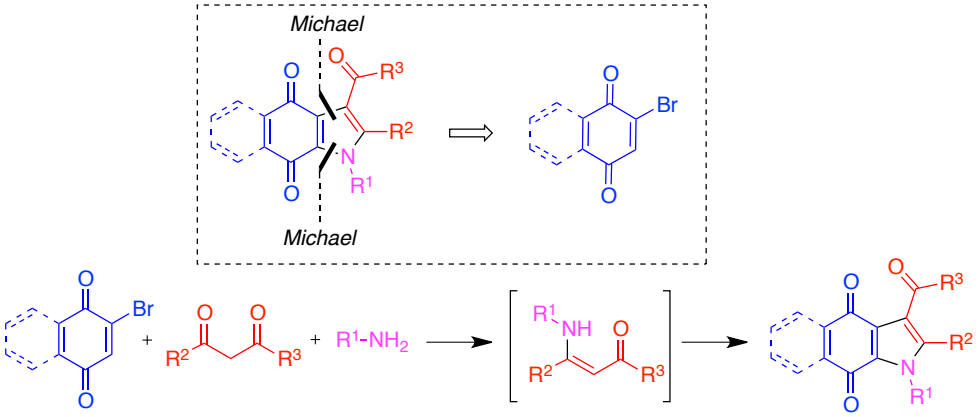
2. Empleo de los productos de tipo Nenitzescu como materiales de partida de reacciones generadoras de complejidad y diversidad estructural, como una aplicación del método conocido como *build-couple-pair* (esquema 2).

8 Revisiones: (a) Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1996**, *67*, 207–343. (b) Michael, J. P.; de Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979. (c) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (d) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463. (e) Bruneau, C.; Renaud, J.-L.; Jerphagnon, T. *Coord. Chem. Rev.* **2008**, *252*, 532.



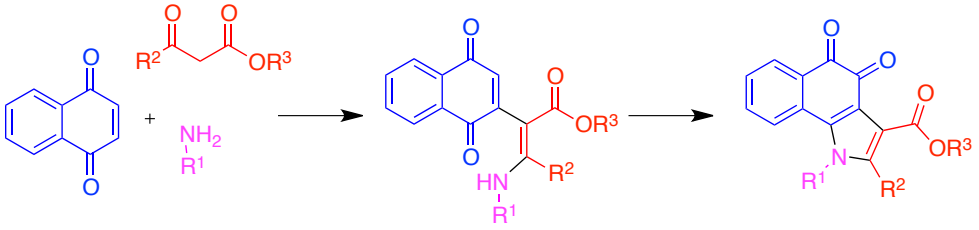

**Esquema 2**

3. Desarrollo de una variante de la reacción de Nenitzescu que permita la síntesis de indolquinones a través de la introducción de un grupo saliente en la quinona de partida (esquema 3).



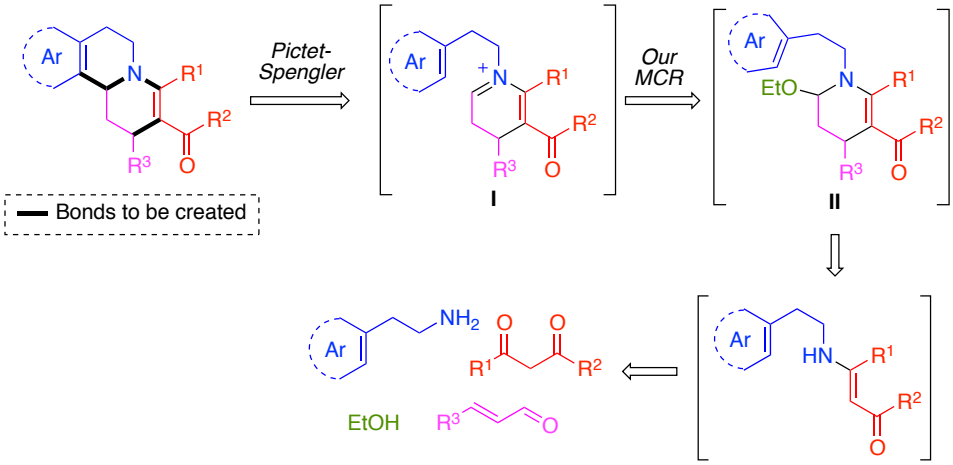

**Esquema 3**

4. Desarrollo de un método en tres componentes para la síntesis de β-enaminones acopladas a nafotoquinona, y su transformación posterior en *orto*-quinonas derivadas del sistema de benzo[*g*]indol, de interés biológico (esquema 4).



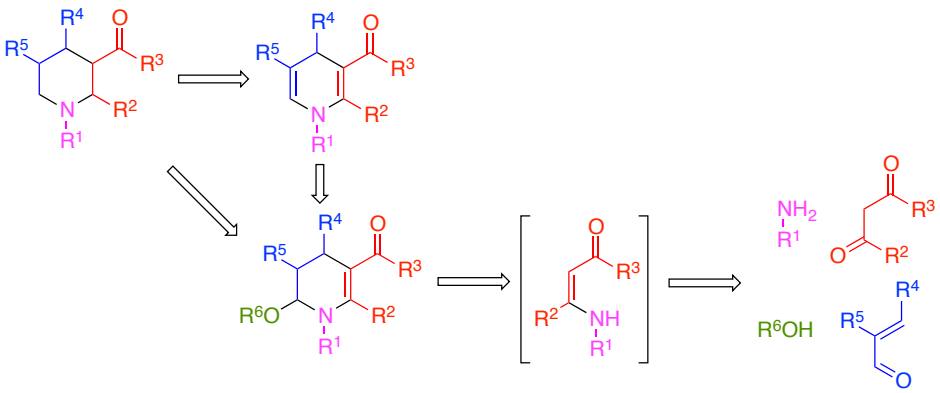

**Esquema 4**

5. Desarrollo de un método para la síntesis de areno[*a*]quinolizinas en una única operación sintética a partir de la combinación de una síntesis multicomponente de 6-etoxi-1,4,5,6-tetrahidropiridinas previamente desarrollada por nuestro grupo con la reacción de Pictet-Spengler (esquema 5).




**Esquema 5**

6. Adaptación de la reacción multicomponente previamente mencionada a la síntesis de 1,4-dihidropiridinas y, a partir de éstas, de piperidinas polisustituidas (esquema 6).




**Esquema 6**

## 3. RESULTADOS Y DISCUSIÓN

### 3.1. Versión multicomponente de la reacción de Nenitzescu

Debido a la enorme importancia del indol como estructura privilegiada en el descubrimiento de fármacos,[9,10] resulta de gran importancia el descubrimiento de nuevos métodos para la síntesis de indoles, así como la mejora de los procedimientos existentes. Fijamos nuestra atención en la reacción de Nenitzescu,[11] nombre que recibe la reacción entre 1,4-benzoquinonas y β-enaminonas para dar 5-hidroxiindoles, debido a que es un método relativamente poco estudiado a causa de la baja estabilidad en medio ácido de las β-enaminonas necesarias como materiales de partida. Esto sugiere que una aproximación multicomponente, en la que estos compuestos se generen *in situ* a partir de precursores más sencillos, puede conducir a una versión más general de la reacción.

Para conseguir este objetivo, era necesario encontrar un catalizador capaz de promover tanto la formación de la β-enaminona como las etapas posteriores del proceso. Tras un proceso de optimización, escogimos el nitrato cérico amónico (CAN)[12] ya que nuestro grupo había demostrado que es un excelente catalizador de la formación de enaminonas a partir de aminas primarias y compuestos 1,3-dicarbonílicos,[13] en condiciones de reflujo en etanol. Los resultados de la reacción a partir de naftoquinona se resumen en el esquema 7 y la tabla 1, que demuestra la posibilidad de

9 Aplicaciones del concepto de estructura privilegiada al descubrimiento de fármacos: (a) Muller, G. *Drug Discovery Today*, **2003**, *8*, 681. (b) Costantino, L.; Barlocco, D. *Curr. Med. Chem.,* **2006**, *13*, 65. (c) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol*. **2010**, *14*, 1.

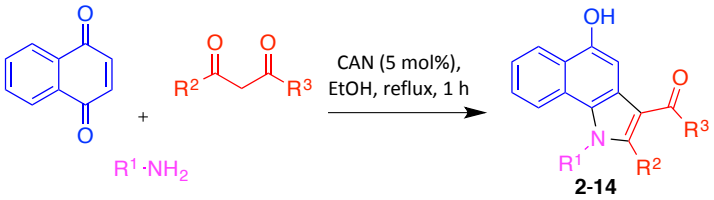
10 Alves, F. R. S.; Barreiro, E. J.; Fraga, C. A. M. *Mini-Rev. Med. Chem.,* **2009**, *9*, 782.

11 Revisión: Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Org. Chem.,* **2008**, *12*, 691.

12 Revisión del empleo de CAN como catalizador en síntesis orgánica: Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.,* **2010**, *110*, 3805.

13 Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Synlett,* **2007**, 881.

emplear β-cetoésteres y β-cetotioésteres como el componente dicarbonílico y aminas primarias alifáticas (entradas 1-8) o anilinas, portadoras indistintamente de grupos donadores o aceptores.




**2-14**

**Esquema 7**

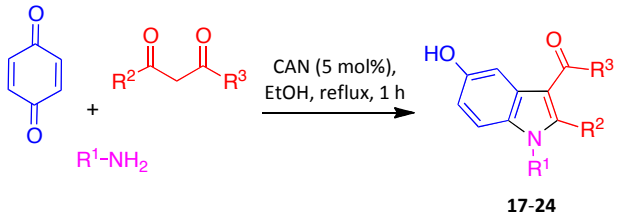
**Tabla 1**

| Entrada | Comp. | $R^1$ | $R^2$ | $R^3$ | Rto. (%) |
|---|---|---|---|---|---|
| 1 | **2** | *n*-Bu | Me | OEt | 93 |
| 2 | **3** | *n*-Bu | Me | OMe | 96 |
| 3 | **4** | $CH_2$-CH=$CH_2$ | Me | OEt | 90 |
| 4 | **5** | $CH_2$-Ph | Me | OEt | 90 |
| 5 | **6** | $CH_2$-CH=$CH_2$ | Me | OMe | 89 |
| 6 | **7** | $CH_2$-CH=$CH_2$ | Me | S-$^t$Bu | 87 |
| 7 | **8** | $CH_2$-C≡CH | Me | S-$^t$Bu | 88 |
| 8 | **9** | $CH_2$-C≡CH | Me | OEt | 75 |
| 9 | **10** | Ph | Me | OEt | 65 |
| 10 | **11** | *p*-$MeOC_6H_4$ | Me | OEt | 55 |
| 11 | **11** | *p*-$MeOC_6H_4$ | Me | OEt | 73[a] |
| 12 | **12** | *p*-$ClC_6H_4$ | Me | OEt | 50 |
| 13 | **12** | *p*-$ClC_6H_4$ | Me | OEt | 76[a] |
| 14 | **13** | *n*-Bu | Me | S-$^t$Bu | 70 |
| 15 | **14** | *n*-Bu | *n*-Pr | OEt | 52 |

[a] A partir de la enaminona aislada (compuesto **15**).

Aunque el empleo de naftoquinona era de interés por ser un material de partida poco estudiado en la reacción de Nenitzescu, investigamos también el empleo de benzoquinona, el sustrato convencional, ya que permite una comparación entre el método multicomponente y el tradicional. Resultaron

los derivados de 5-hidroxiindol **17**-**24**, normalmente con rendimientos entre buenos y muy buenos (esquema 8 y tabla 2).



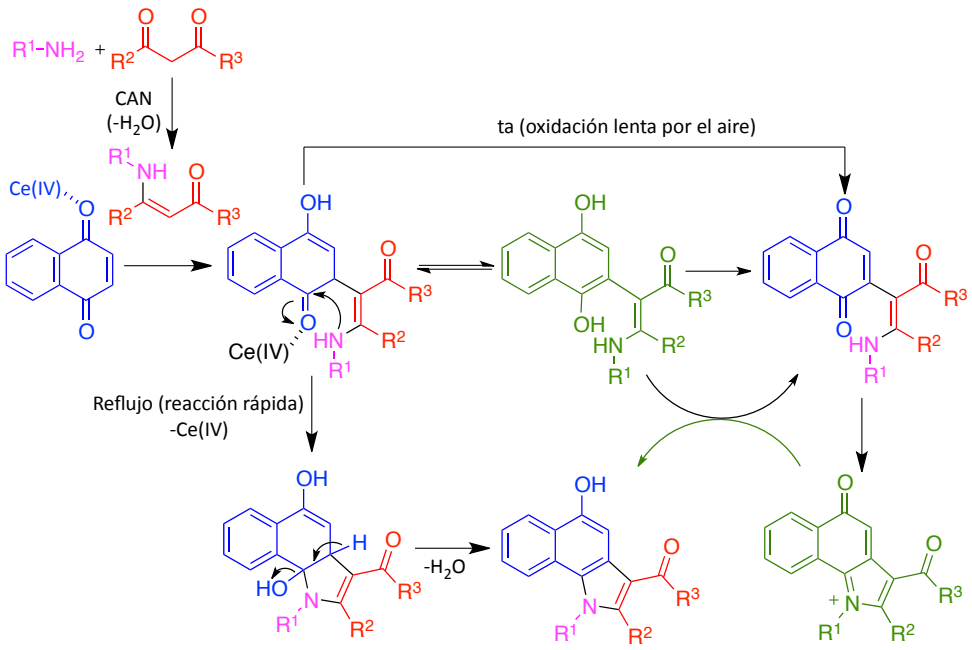

**17-24**

**Esquema 8**

**Tabla 2**

| Entrada | Comp. | $R^1$ | $R^2$ | $R^3$ | Rto. (%) |
|---|---|---|---|---|---|
| 1 | **17** | *n*-Bu | Me | OEt | 78 |
| 2 | **18** | $CH_2$-CH=$CH_2$ | Me | OEt | 75 |
| 3 | **19** | $CH_2$-Ph | Me | OEt | 73 |
| 4 | **20** | $CH_2$-C≡CH | Me | OEt | 69 |
| 5 | **21** | *n*-Bu | Me | S-$^t$Bu | 86 |
| 6 | **22** | $CH_2$-CH=$CH_2$ | Me | S-$^t$Bu | 81 |
| 7 | **23** | *n*-Bu | *n*-Pr | OEt | 82 |
| 8 | **24** | $CH_2$-CH=$CH_2$ | *n*-Pr | OEt | 78 |

Un estudio basado en el aislamiento de algunos intermedios clave nos lleva a proponer para nuestro proceso multicomponente el mecanismo mostrado en el esquema 9, que difiere en algunos aspectos del que normalmente se acepta para la reacción de Nenitzescu.[11] Proponemos que los intermedios representados en verde, que constituyen etapas del mecanismo redox convencional, no se forman en nuestro caso.

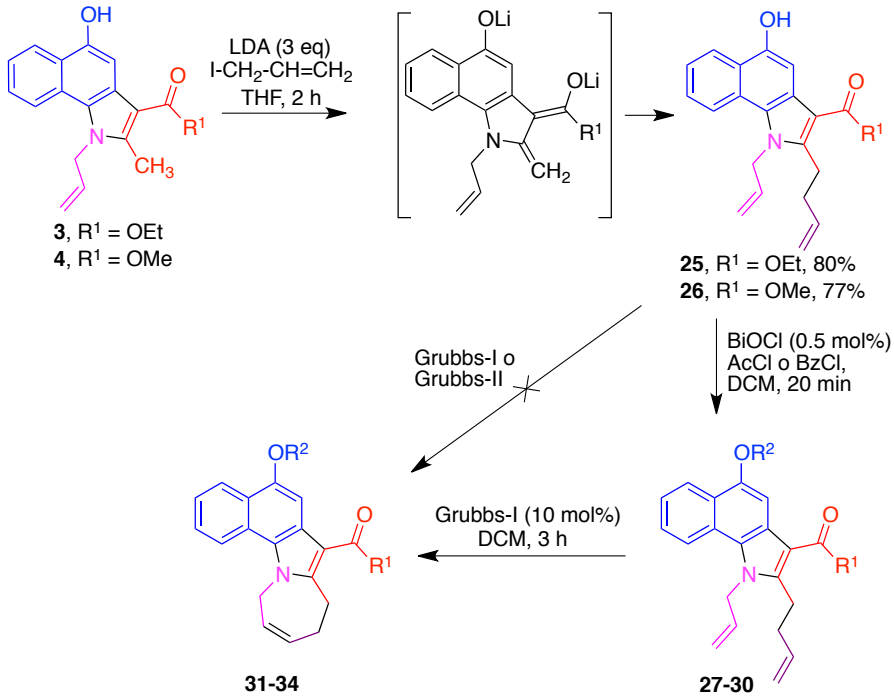



**Esquema 9**

En relación con el segundo de nuestros objetivos, investigamos también la manipulación posterior de los productos de Nenitzescu para dar lugar a heterociclos complejos. De hecho, la combinación de reacciones multicomponente con transformaciones postcondensación capaces de generar complejidad estructural constituye la base del procedimiento de síntesis orientada a la diversidad conocido como *build-couple-pair*.[14] Así, una reacción de metátesis con cierre de anillo entre sustituyentes olefínicos presentes en el nitrógeno y la posición vecina debería dar lugar a compuestos tetracíclicos poco habituales, con un átomo de nitrógeno en una posición de fusión. Para trasladar esta idea a la práctica, llevamos a cabo la desprotonación del grupo metilo de los N-alil derivados **4** and **6** con LDA, seguida de alilación o propargilación para dar los compuestos **25** y **26**,

14 (a) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56. (b) Schreiber, S. L. *Nature* **2009**, *457*, 153–154.

cuya metátesis fue imposible en todas las condiciones ensayadas. En cambio, los *O*-acil derivados **27**-**30** experimentaron una fácil ciclación en presencia del catalizador de Grubbs de primera generación para dar los compuestos **31**-**34**, derivados de un sistema heterocíclico previamente desconocido, el azepino[1,2-*a*]benzo[*g*]indol, y que están relacionados estructuralmente con pirrolo[1,2-*a*]azepinas bioactivas[15] (esquema 10 y tabla 3).




**Esquema 3.10**

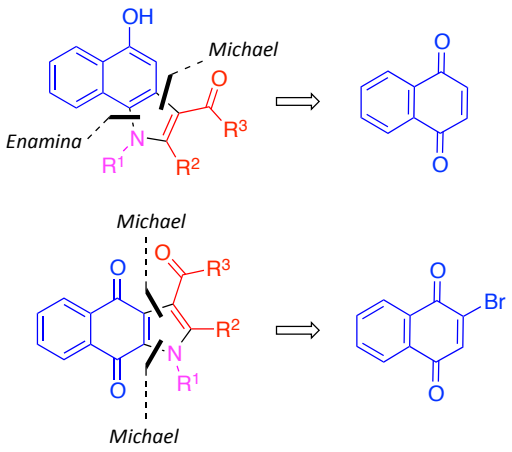
15 Bonanni, M.; Marradi, M.; Cardona, F.; Cicchi, S.; Goti, A. *Beilstein J. Org. Chem.*, **2007**, *3*, 44.

**Tabla 3**

| Entrada | $R^1$ | $R^2$ | Alilación | | RCM | |
|---|---|---|---|---|---|---|
| | | | Comp. | Rto. (%) | Comp. | Rto. (%) |
| 1 | OEt | Ac | **27** | 95 | **31** | 80 |
| 2 | OMe | Ac | **28** | 94 | **32** | 77 |
| 3 | OEt | Bz | **29** | 80 | **33** | 77 |
| 4 | OMe | Bz | **30** | 82 | **34** | 76 |

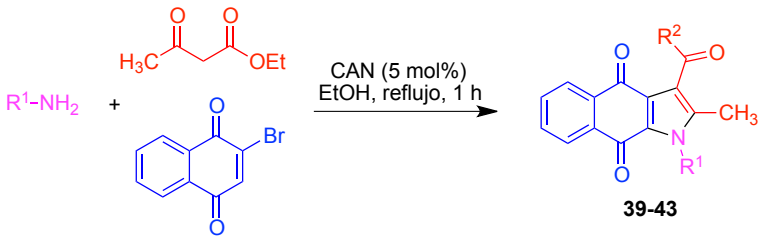
### 3.2. Síntesis de indoles fusionados lineales a través de un proceso dominó Michael-Michael

La consideración de nuestra propuesta mecanística para la reacción de Nenitzescu muticomponente nos llevó a plantear la posibilidad de desviar la secuencia de reacciones hacia un proceso Michael-Michael. Para ello, consideramos necesario incrementar la reactividad del doble enlace quinónico por introducción de un grupo saliente en su posición C-2, para lo cual decidimos emplear bromobenzoquinona como compuesto de partida. Este planteamiento se resume en el esquema 11.




**Esquema 11**

Tras el correspondiente trabajo de optimización, se encontraron unas condiciones adecuadas para lograr la transformación deseada, que se resumen en el esquema 12 y la tabla 4.




**Esquema 12**

**Tabla 4**

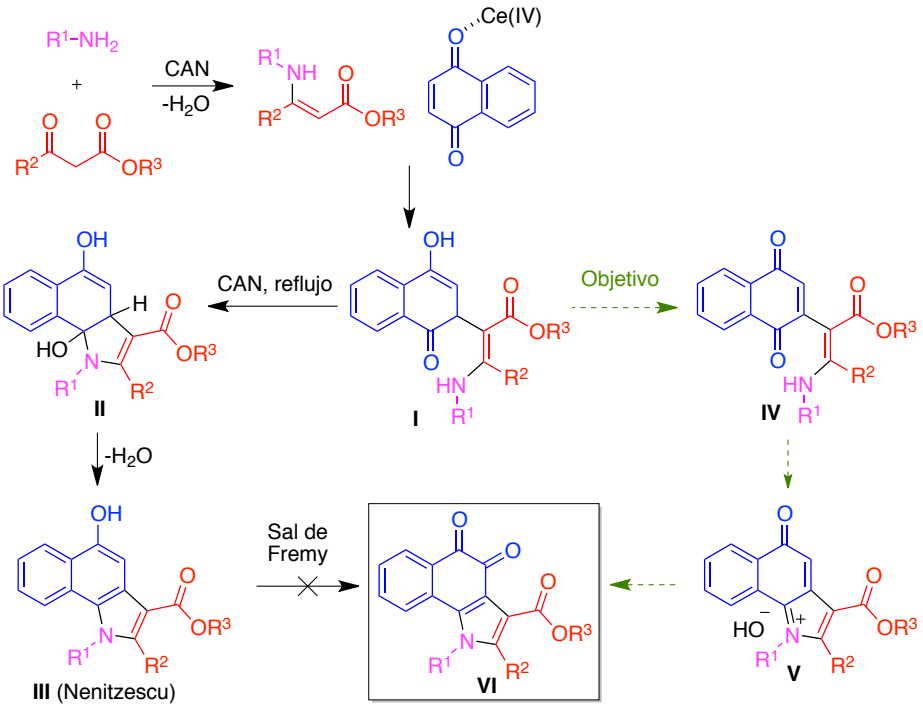
| Entrada | Comp. | $R^1$ | $R^2$ | Rto. (% ) |
|---|---|---|---|---|
| 1 | **39** | *n*-Bu | OEt | 54[a] |
| 2 | **41** | *n*-Bu | Me | 67 |
| 3 | **42** | $CH_2$-Ph | Me | 51 |
| 4 | **43** | $CH_2$-CH=$CH_2$ | Me | 44 |
| 5 | **44** | $CH_2$-C≡CH | Me | 42 |

### 3.3. Síntesis de *orto*-quinonas derivadas del sistema de benzo[*g*]indol

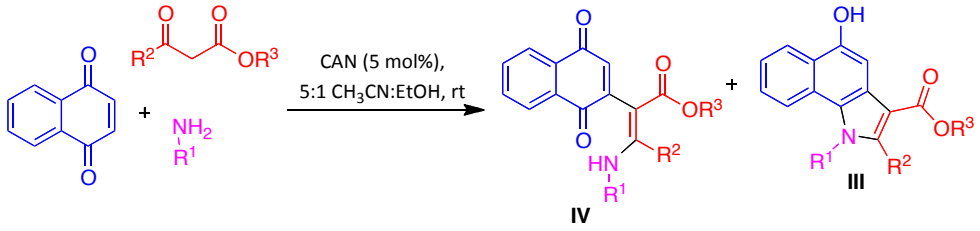
A causa de la gran importancia biológica de las quinonas, nos pareció interesante desarrollar una ruta hacia *orto*-quinonas indólicas basada en una variación de nuestra reacción de Nenitzescu. Para ello, era necesario desviar ésta hacia la producción de aductos de Michael oxidados **IV**, que a su vez deberían ser precursores de derivados de iminio **V** que, a su vez, generarían las quinonas deseadas **VI**, a las que no habíamos podido acceder por oxidación de los productos de Nenitzescu (esquema 13).

Como etapa inicial para alcanzar nuestro objetivo, encontramos que la reacción en una mezcla 5:1 de acetonitrilo y etanol entre aminas primarias, β-cetoésteres y naftoquinona en presencia de CAN (5 %), a temperatura ambiente y en un matraz expueso al aire para facilitar la etapa de oxidación

necesaria para acceder a **IV**, proporcionaba este compuesto como producto mayoritario, junto con cantidades variables del producto de tipo Nenitzescu (esquema 14 y tabla 5). A partir de los compuestos **IV** aislados, un simple reflujo en etanol en presencia de CAN proporcionó las orto-quinonas deseadas, de nuevo acompañadas por cantidades variables del producto de tipo Nenitzescu (esquema 15 y tabla 6).



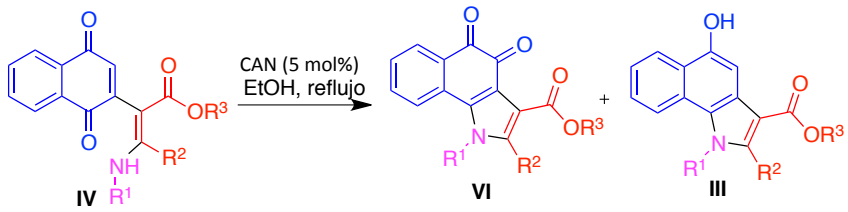

**Esquema 13**




**Esquema 14**

**Tabla 5**

| Entrada | Comp. | $R^1$ | $R^2$ | $R^3$ | Tiempo, h | IV/III | IV (%) |
|---|---|---|---|---|---|---|---|
| 1 | **40** | *n*-Bu | Me | Et | 1.5 | 85:15 | 65 |
| 2 | **45** | *n*-Bu | Me | $^t$Bu | 1 | 80:20 | 68 |
| 3 | **46** | $CH_2$-CH=$CH_2$ | Me | Et | 1 | 75:25 | 62 |
| 4 | **47** | *n*-Bu | Me | Me | 1.5 | 75:25 | 60 |
| 5 | **48** | *n*-Bu | Me | $CH_2$-CH=$CH_2$ | 1.5 | 78:22 | 65 |
| 6 | **49** | *n*-Pr | Me | Et | 1 | 70:30 | 58 |
| 7 | **50** | $CH_2$-Ph | Me | Et | 1.5 | 65:35 | 62 |
| 8 | **51** | *n*-Bu | n-Pr | Et | 1 | 65:35 | 60 |




**Esquema 15**

**Tabla 6**

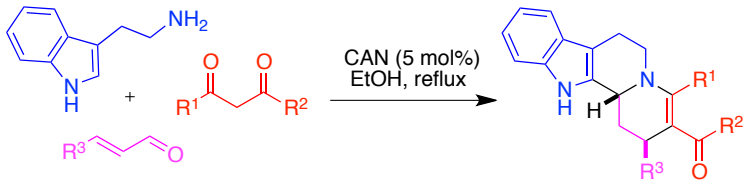
| Entrada | Comp. | $R^1$ | $R^2$ | $R^3$ | Tiempo, h | VI/III | VI (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **52** | *n*-Bu | Me | Et | 2 | 75:25 | 61 |
| 2 | **53** | *n*-Bu | Me | $^t$Bu | 1 | 70:25 | 55 |
| 3 | **54** | $CH_2$-CH=$CH_2$ | Me | Et | 2 | 85:15 | 56 |
| 4 | **55** | *n*-Bu | Me | Me | 0.5 | 65:35 | 58 |
| 5 | **56** | *n*-Bu | Me | $CH_2$-CH=$CH_2$ | 1 | 73:27 | 55 |
| 6 | **57** | *n*-Pr | Me | Et | 2 | 75:25 | 59 |
| 7 | **58** | $CH_2$-Ph | Me | Et | 2 | 80:20 | 57 |
| 8 | **59** | *n*-Bu | *n*-Pr | Et | 1 | 85:15 | 60 |

### 3.4. Sintesis multicomponente de areno[*a*]quinolizinas

Como ya se ha mencionado, nuestro grupo ha desarrollado una reacción en cuatro componentes que permite la síntesis de 1-alquil-6-etoxi-1,4,5,6-tetrahidropiridinas a partir de aminas primarias, compuestos β-dicarbonílicos, aldehídos α,β-insaturados y alcoholes primarios.[16] Uno de nuestros objetivos era la combinación de esta reacción con una reacción de Pictet–Spengler, dando lugar a un proceso dominó que permitiera la preparación directa de areno[*a*]quinolizinas de interés biológico a partir de precursores abiertos. Tras ensayar infructuosamente el empleo de acroleína, llevamos a cabo la reacción entre triptamina, compuestos β-dicarbonílicos y derivados de cinamaldehído en etanol a reflujo, accediendo a una amplia serie de derivados de indolo[2,3-*a*]quinolizina (esquema 17 y tabla 7). Aunque llevamos a cabo al mayor parte de los experimentos con acetoacetato de etilo, disponible comercialmente y muy barato, también demostramos la posibilidad de tener cadenas más

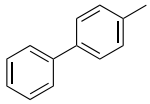
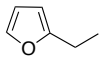
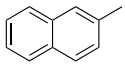
16 Sridharan, V.; Maiti, S.; Menéndez, J. C. *Chem. Eur. J.* **2009**, *15*, 4565.

complejas en la posición 4 del producto final, como por ejemplo en el caso del compuesto **76**, procedente de un β-cetoéster obtenido por tratamiento del dianión del acetoacetato de etilo con bromuro de 2,4-hexadien-1-ilo.

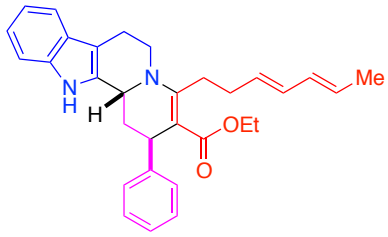



**Esquema 17**

**Tabla 7**

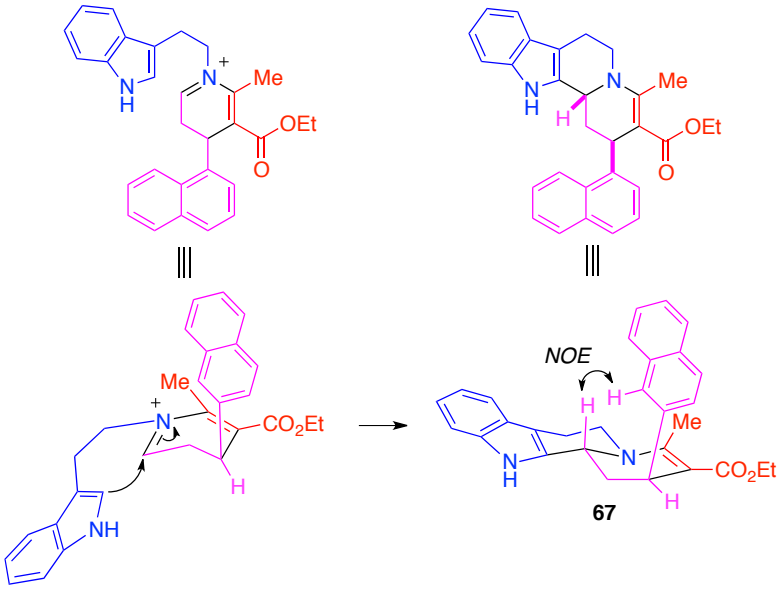
| Entrada | Comp. | $R^1$ | $R^2$ | $R^3$ | t (h) | Rto. (%) |
|---|---|---|---|---|---|---|
| 1 | **62** | Me | OEt | Ph | 1.5 | 86 |
| 2 | **63** | Me | OMe | Ph | 1 | 88 |
| 3 | **64** | Me | OEt |  | 1.5 | 86 |
| 4 | **65** | Me | OEt | 4-$ClC_6H_4$ | 1.5 | 88 |
| 5 | **66** | Me | OEt | 4-$MeOC_6H_4$ | 1.5 | 85 |
| 6 | **67** | Me | OEt | 2-$NO_2C_6H_4$ | 1.5 | 28 |
| 7 | **68** | Me | OEt |  | 1 | 77 |
| 8 | **69** | Me | OEt |  | 1 | 92 |
| 9 | **70** | Me | OEt | Me | 1 | 62 |
| 10 | **71** | Me | OEt | *n*-Pr | 1 | 40 |
| 11 | **72** | Me | S-$^t$Bu | Ph | 1 | 70 |
| 12 | **73** | Me | O-$^t$Bu | Ph | 1 | 68 |
| 13 | **74** | *n*-Pr | OEt | Ph | 1 | 50 |
| 14 | **75** | Me | Me | Ph | 1.5 | 48 |
| 15 | **75** | Me | Me | Ph | 12 | 72 |
| 16 | **75** | Me | Me | Ph | 2 | 80[a] |

[a] En este caso, se empleó un 15 % de CAN




**76**

La configuración relativa de los estereocentros se dedujo a partir de estudios de efectos NOE del compuesto **69**. El producto procede del ataque del anillo de indol al catión aciliminio por la cara opuesta al sustituyente naftilo (esquema 18).

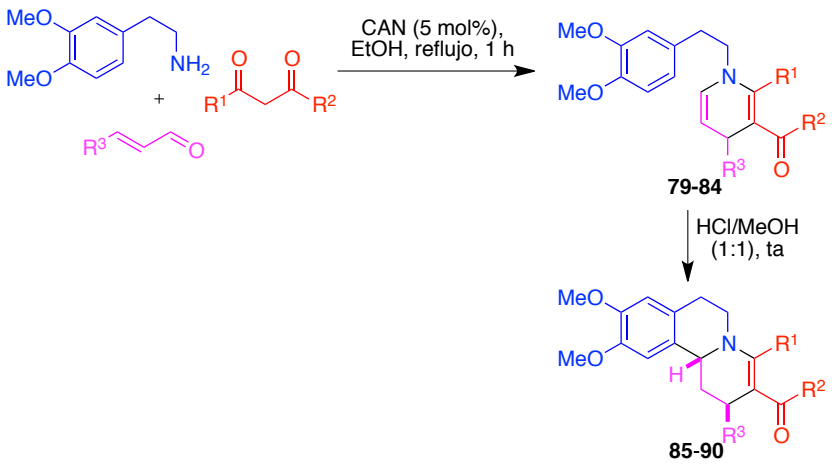



**67**

**Esquema 18**

Investigamos también la aplicación de nuestro método a la síntesis de derivados de benzo[*a*]quinolizina, utilizando para ello 3,4-dimetoxifenetilamina como amina de partida. Los productos de reacción se identificaron como los derivados de dihidropiridina **79**-**84**, lo que se atribuyó a a una menor nucleofilia del anillo aromático. Estos compuestos

pudieron ciclarse a las correspondientes benzo[*a*]quinolizinas **85**-**90** por tratamiento con una mezcla 1:1 de HCl al 35% y metanol a temperatura ambiente (esquema 19 y tabla 8), aunque el éster *terc*-butílico **80** fue inestable en estas condiciones.




**Esquema 19**

**Tabla 8**

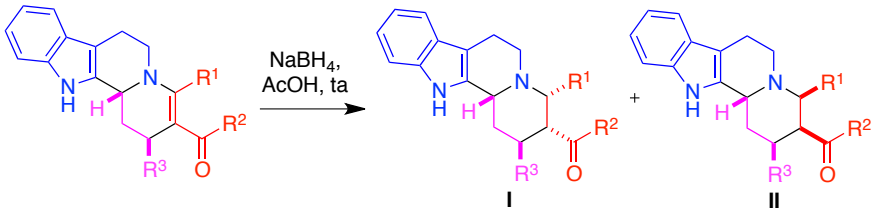
| Entrada | $R^1$ | $R^2$ | $R^3$ | Dihidropiridinas | | Benzo[*a*]quinolizinas | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Comp. | Rto., %[a] | Comp. | Tiempo, h | Rto., % |
| 1 | Me | OEt | Ph | **79** | 70 | **85** | 2 | 75 |
| 2 | Me | O-$^t$Bu | Ph | **80** | 72 | **86** | 2 | 0 |
| 3 | Me | OEt | 4-Cl$C_6H_4$ | **81** | 68 | **87** | 2 | 76 |
| 4 | Me | OEt | 4-MeO$C_6H_4$ | **82** | 65 | **88** | 4 | 77 |
| 5 | Me | OEt | Me | **83** | 62 | **89** | 8 | 63 |
| 6 | *n*-Pr | OEt | Ph | **84** | 60 | **90** | 2 | 60 |

Finalmente, estudiamos la reducción de nuestros derivados a las correspondientes indolo[2,3-*a*]quinolizidinas y benzo[*a*]quinolizidinas, utilizando para ello triacetoxiborohidruro de sodio ($Na(OAc)_3BH$, STAB),

generado *in situ* a partir de borohidruro de sodio y ácido acético.[17] Este reactivo es un reductor suave en el que el efecto aceptor de los tres grupos acetoxi estabiliza el enlace B-H[18] y que es capaz de introducir dos hidrógenos en disposición *cis* en dobles enlaces pertenecientes a carbamatos vinílogos, semejantes a los presentes en nuestros sustratos.[19]

La reducción de las indolo[2,3-*a*]quinolizinas por este método dio buenos rendimientos de los diastereoisómeros **I** y **II**, que en general se obtuvieron en una relación aproximadamente 40:60 (esquema 20 y tabla 9). Los productos mayoritarios se identificaron como los derivados todo-*cis* **II**, en los que la reducción tiene lugar por la cara opuesta al sustituyente $R^3$. La configuración relativa de los diastereoisómeros **I** y **II** se estableció a partir de sus datos espectroscópicos de los compuestos **91** y **92**, como se resume en la figura 1.

La reducción de los derivados de benzo[*a*]quinolizina dio un resultado similar, proporcionando los derivados de benzo[*a*]quinolizidina **III** y **IV**. De nuevo, los productos mayoritarios fueron los compuestos **IV**, procedentes de la reducción por la cara del doble enlace opuesta al sustituyente $R^3$ (esquema 21 y tabla 10).



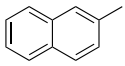

**Esquema 20**

17 Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328.

18 Revisiones: (a) Abdel-Magid, A.; Mehrman, S. J. *Org. Proc. Res. Devel.* **2006**, 10, 971. (b) Gribble, G. W. *Chem. Soc. Rev.* **1998**, 27, 395.

19 (a) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328. (b) Sridharan, V.; Menéndez, J. C. *Org. Lett.* **2008**, *10*, 4303.

**Tabla 9**

| Entrada | Comps. (I,II) | $R^1$ | $R^2$ | $R^3$ | t (h) | Rto. (%) | I/II |
|---|---|---|---|---|---|---|---|
| 1 | **91,92** | Me | OEt | Ph | 2 | 86 | 40:60 |
| 2 | **93,94** | Me | OEt | 4-$PhC_6H_4$ | 5 | 85 | 46:54 |
| 3 | **95,96** | Me | OEt | 4-$ClC_6H_4$ | 2 | 89 | 40:60 |
| 4 | **97,98** | Me | OEt | 4-$MeOC_6H_4$ | 2 | 90 | 39:61 |
| 5 | **99,100** | Me | Me | Ph | 3 | 73 | 47:53 |
| 6 | **101,102** | Me | OEt |  | 3 | 80[c] | 39:61 |
| 7 | **103,104** | Me | S-$^t$Bu | Ph | 1.3 | 85 | 39:61 |
| 8 | **105,106** | Me | O-$^t$Bu | Ph | 1.3 | 80 | 48:52 |
| 9 | **107,108** | Me | OEt |  | 72[a] | 58[c] | 33:57 |
| 10 | **109,110** | Me | OEt | Me | 2 | 60[c] | 42:58 |
| 11 | **111,112** | Me | OEt | *n*-Pr | 2 | 68[c] | 40:60 |
| 12 | **113,114** | *n*-Pr | OEt | Ph | 36 | 65[c] | 35:65 |

[a] Se recuperó un 18% de compuesto de partida **69**. [b] Se recuperó un 22% de compuesto de partida **74**.

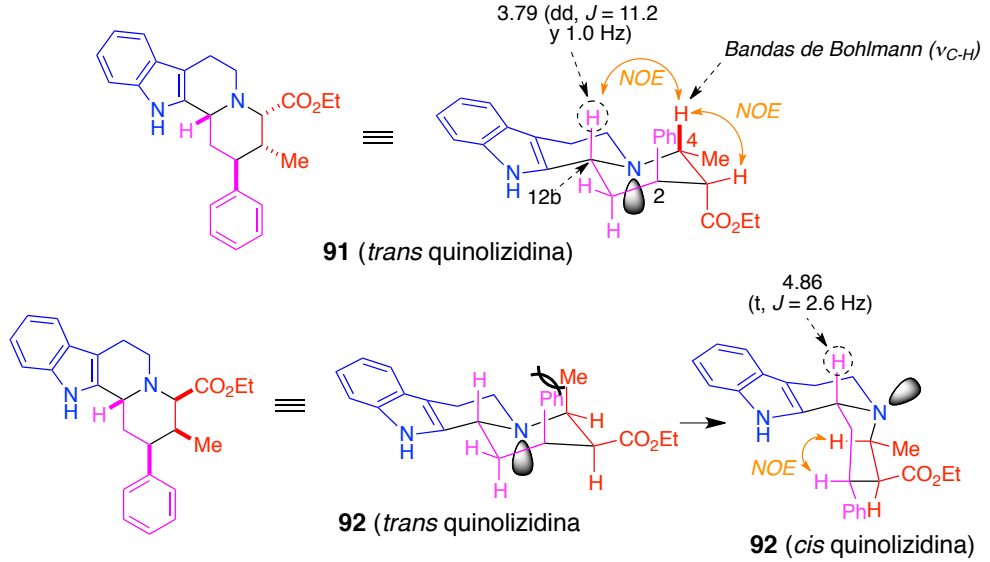
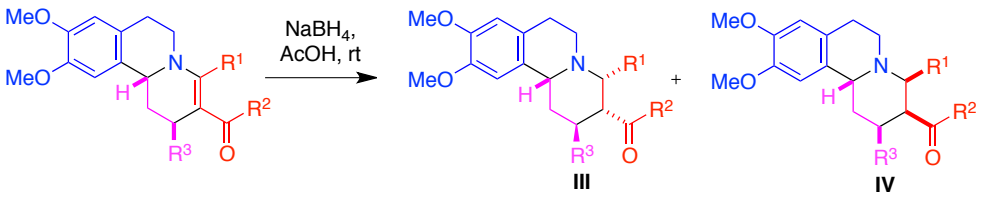



**Figura 1**




**Esquema 21**

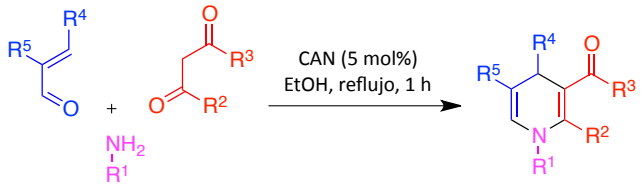
**Tabla 10**

| Entrada | Comps. (III,IV) | $R^1$ | $R^2$ | $R^3$ | Rto. (%) | III/IV |
|---|---|---|---|---|---|---|
| 1 | **115,116** | Me | OEt | Ph | 90 | 38:62 |
| 2 | **117,118** | Me | OEt | *p*-$ClC_6H_4$ | 92 | 35:65 |
| 3 | **119,120** | Me | OEt | *p*-$MeOC_6H_4$ | 82 | 32:68 |
| 4 | **121,122** | *n*-Pr | OEt | Ph | 78 | 35:65 |
| 5 | **123,124** | Me | OEt | Me | 79 | 35:65 |

## 3.5. Síntesis diastereoselectiva de piperidinas basada en una reacción multicomponente

### *3.5.1. Síntesis de materiales de partida*

Ya se ha mencionado que la reacción entre aminas primarias, aldehídos α,β-insaturados, compuestos β-dicarbonílicos y alcoholes a temperatura ambiente proporciona 6-alcoxi-1,4,5,6-tetrahidropiridinas.[16] Otros miembros de nuestro grupo han transformado estos compuestos en 1,4-dihidropiridinas en condiciones de reflujo en presencia de alúmina neutra (grado de actividad I) suspendida en acetonitrilo o etanol.[20] Este

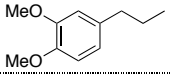
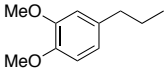
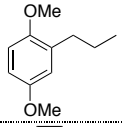
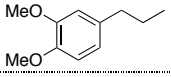
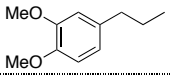
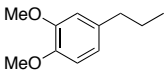
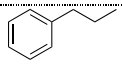
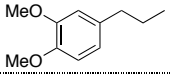
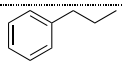
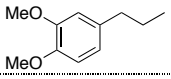
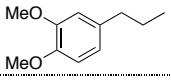
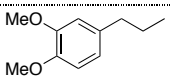
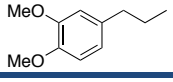



**Esquema 22**

20 (a) Maiti, S.; Menéndez, J. *Synlett* **2009**, 2249. (b) Maiti, S.; Sridharan, V.; Menéndez, J. C. *J. Comb. Chem.* **2010**, *12*, 713.

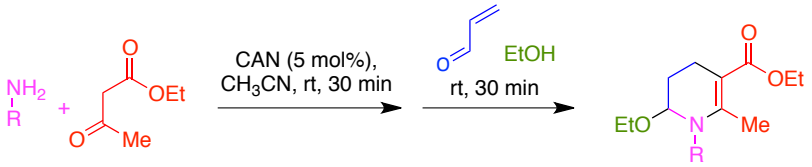
protocolo plantea el problema de separar los productos de la alúmina, lo que requiere lavados repetidos y en caliente con disolventes polares. En el presente trabajo (esquema 22 y tabla 11), hemos mejorado este procedi-

**Tabla 11**

| Entrada | Comp. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Rto. (%) |
|---|---|---|---|---|---|---|---|
| 1 | **79** |  | Me | OEt | Ph | H | 70 |
| 2 | **80** |  | Me | O-$^t$Bu | Ph | H | 72 |
| 3 | **125** |  | Me | OEt | Ph | H | 66 |
| 4 | **126** |  | Me | OEt | Ph | H | 66 |
| 5 | **84** |  | *n*-Pr | OEt | Ph | H | 60 |
| 6 | **127** |  | Me | OEt | *p*-$MeC_6H_4$ | H | 62 |
| 7 | **82** |  | Me | OEt | *p*-$MeOC_6H_4$ | H | 65 |
| 8 | **128** |  | Me | OEt | *p*-$MeOC_6H_4$ | H | 68 |
| 9 | **129** | *n*-Pr | Me | O-$^t$Bu | *p*-$NO_2C_6H_4$ | H | 70 |
| 10 | **130** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H | 78 |
| 11 | **131** | Bn | Me | OEt | *p*-$NO_2C_6H_4$ | H | 72 |
| 12 | **132** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H | 86 |
| 13 | **133** | *n*-Bu | Me | OEt | *o*-$NO_2C_6H_4$ | H | 68 |
| 14 | **81** |  | Me | OEt | *p*-$ClC_6H_4$ | H | 68 |
| 15 | **134** |  | Me | OEt | Et | Me | 64 |
| 16 | **83** |  | Me | OEt | Me | H | 62 |
| 17 | **135** | Bn | Me | OEt | Me | H | 55 |
| 18 | **136** | *n*-Pr | Me | OEt | Me | H | 68 |
| 19 | **137** | *n*-Bu | Me | OEt | Me | H | 65 |
| 20 | **138** |  | Me | OEt | H | Me | 53 |

miento de síntesis al descubrir que, para el caso de los derivados sustituidos en posición 4 o 5, se obtienen buenos rendimientos de dihidropiridinas simplemente llevando a cabo la reacción multicomponente en etanol a reflujo. Esta diferencia de comportamiento sugiere que, en estas nuevas condiciones en las que no se aísla el derivado de 6-alcoxi-1,4,5,6-tetrahidropiridina, la reacción de eliminación tiene lugar sobre otra especie, probablemente el 6-hidroxi derivado que se genera en la etapa anterior del mecanismo.

Por otra parte, hemos aislado algunas 6-alcoxi-1,4,5,6-tetrahidropiridinas representativas para estudiar también su reducción (esquema 23 y figura 2).




**Esquema 23**

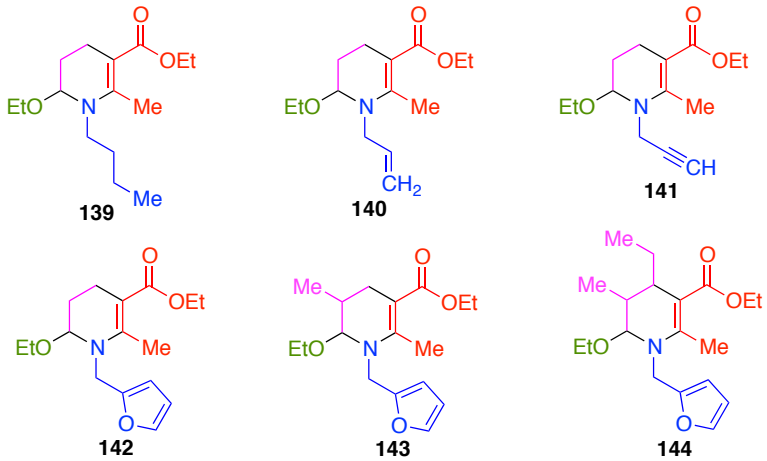
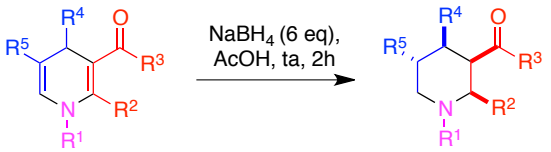


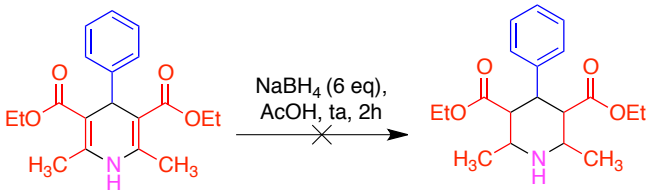

**Figura 2**

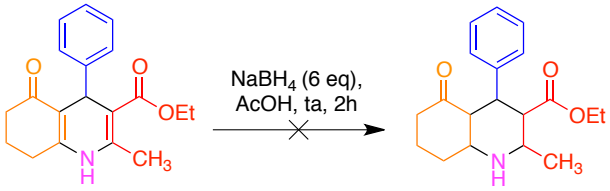
### *3.5.2. Síntesis de piperidinas*

El tratamiento de los derivados de 1,4-dihidropiridina con triacetoxiborohidruro sódico, generado *in situ* a partir de borohidruro sódico y ácido acético, condujo de forma completamente diastereoselectiva a los derivados de piperidina esperados, que pueden ser portadores de hasta cinco sustituyentes y una serie de grupos funcionales (esquema 24 y tabla 12). Los rendimientos fueron satisfactorios, estando normalmente en el intervalo 75-90%. En cambio, el método falló para derivados de 1,4-dhihidropiridina para los que ambos dobles enlaces estaban incluidos en subestructuras de carbamato o amida viníloga (esquema 25). Este comportamiento sugiere que es necesario un paso inicial de protonación, que en estos sustratos no es posible a causa de la baja densidad electrónica de su nitrógeno.




**Esquema 24**

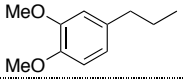
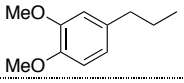
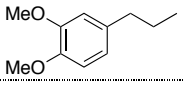
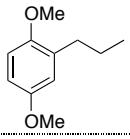
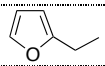
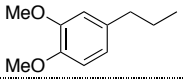
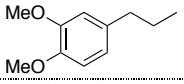
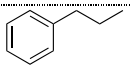
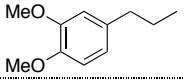
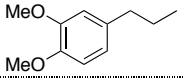
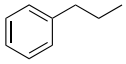
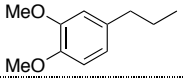
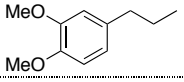
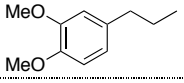


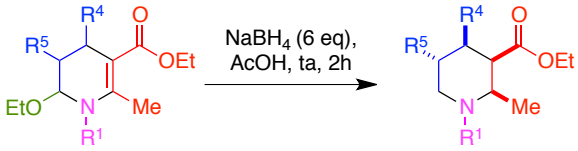

**165**

**Esquema 25**

**Tabla 12**

| Entrada | Comp. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Rto. (%) |
|---|---|---|---|---|---|---|---|
| 1 | **145** |  | Me | OEt | Ph | H | 88 |
| 2 | **146** |  | *n*-Pr | OEt | Ph | H | 79 |
| 3 | **147** |  | Me | O-$^t$Bu | Ph | H | 84 |
| 4 | **148** |  | Me | OEt | Ph | H | 78 |
| 5 | **149** |  | Me | OEt | Ph | H | 92 |
| 6 | **150** |  | Me | OEt | *p*-$MeC_6H_4$ | H | 78 |
| 7 | **151** |  | Me | OEt | *p*-$MeOC_6H_4$ | H | 71 |
| 8 | **152** |  | Me | OEt | *p*-$MeOC_6H_4$ | H | 68 |
| 9 | **153** |  | Me | OEt | *p*-$ClC_6H_4$ | H | 90 |
| 10 | **154** | Bn | Me | OEt | *p*-$NO_2C_6H_4$ | H | 78 |
| 11 | **155** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H | 87 |
| 12 | **156** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H | 86 |
| 13 | **157** | *n*-Pr | Me | O-$^t$Bu | *p*-$NO_2C_6H_4$ | H | 82 |
| 14 | **158** | *n*-Bu | Me | OEt | *o*-$NO_2C_6H_4$ | H | 79 |
| 15 | **159** |  | Me | OEt | Et | Me | 62 |
| 16 | **160** |  | Me | OEt | Me | H | 75 |
| 17 | **161** | Bn | Me | OEt | Me | H | 77 |
| 18 | **162** |  | Me | OEt | H | Me | 67 |
| 19 | **163** | *n*-Pr | Me | OEt | Me | H | 72 |
| 20 | **164** | *n*-Bu | Me | OEt | Me | H | 76 |

La reducción de los derivados de 6-alcoxi-1,4,5,6-tetrahidropiridina dio resultados muy similares a la de los derivados de dihidropiridina (esquema 26 y tabla 13).




**Esquema 26**

**Tabla 13**

| Entrada | Comp. | $R^1$ | $R^4$ | $R^5$ | Rto. (%) |
|---|---|---|---|---|---|
| 1 | **166** | $CH_2$=CH-$CH_2$- | H | H | 78 |
| 2 | **167** | HC≡C-$CH_2$- | H | H | 75 |
| 3 | **168** |  | H | Me | 82 |
| 4 | **169** |  | Et | Me | 71 |
| 5 | **170** |  | H | H | 90 |
| 6 | **171** | *n*-Bu- | H | H | 80 |

El estudio estereoquímico de las piperidinas se llevó a cabo en el compuesto **169**, y se basa en los experimentos NOE resumidos en la figura 3, que indican una configuración relativa todo-*cis* para los sustituyentes en C-2, C-3 y C-4, mientras que el de C-5 es *trans* respecto a los otros. De esta

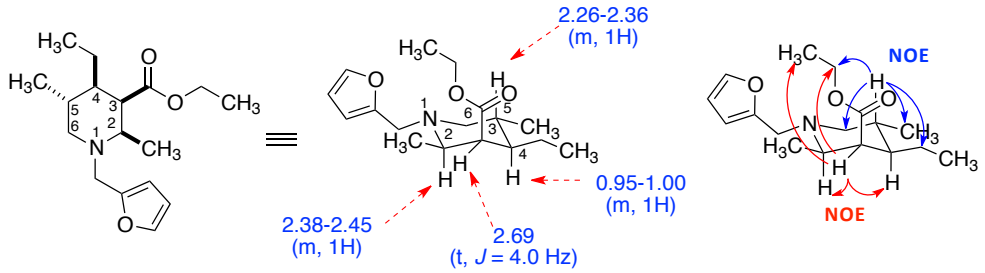
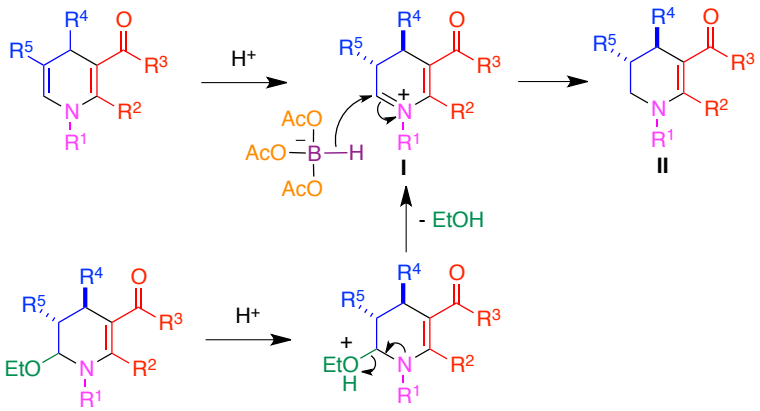



**Figura 3**

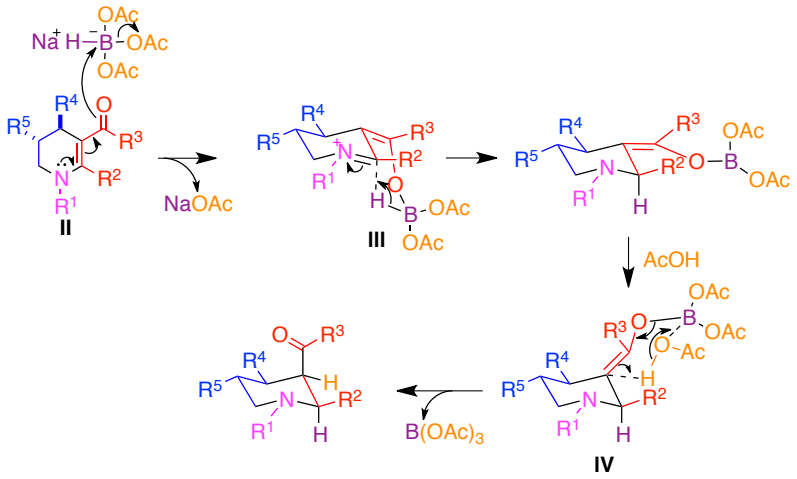
forma, todos los sustituyentes son ecuatoriales excepto el grupo éster de la posición C-3, que es axial.

En cuanto al mecanismo de la reducción de las dihidropiridinas, proponemos que se inicia mediante la protonación del doble enlace más nucleófilo (C5-C6), que tiene lugar de modo que $R^4$ y $R^5$ terminan en una disposición *trans* diecuatorial. En las reacciones que parten de 6-alcoxi-1,4,5,6-tetrahidropiridinas, se llega al mismo intermedio (**I**) por protonación del grupo 6-etoxi y pérdida de una molécula de etanol. La reducción del grupo iminio de **I** por el donador de hidruro conduce a **II** (esquema 27).




**Esquema 27**

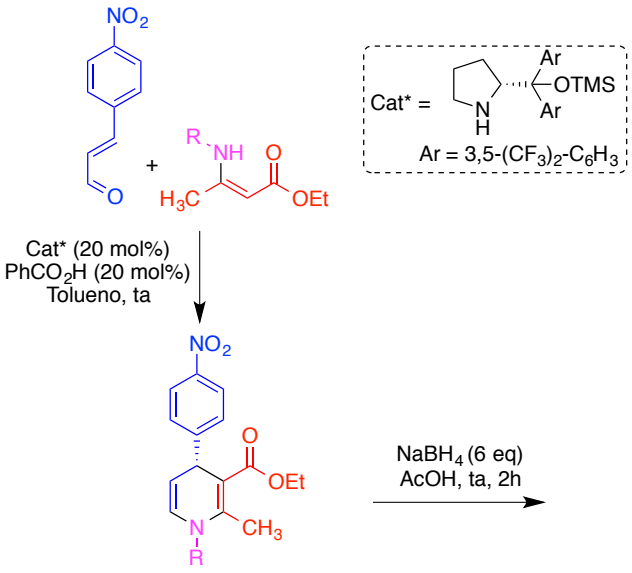
En etapas posteriores, tiene lugar la reducción del doble enlace C=C del grupo carbamato vinílogo de **II**. El reactivo empleado da lugar a reducciones *cis*, a través del mecanismo indicado en en esquema 28 que supone una coordinación inicial del oxígeno carbonílico del éster (**III**), seguida de transferencia intramolecular de hidruro para dar **IV**. En el paso final, el enolato de boro es protonado ecuatorialmente por una molécula de ácido acético y se pierde triacetato de boro.




**Esquema 28**

También investigamos la integridad de los estereocentros en el curso de la reducción con el triacetoxiborohidruro sódico. Para ello, preparamos dos dihidropiridinas quirales utilizando un método bibliográfico[21] basado en la reacción entre β-enaminonas y derivados de cinamaldehído en presencia del catalizador de Hayashi-Jørgensen. Los compuestos **172** y **173** se obtuvieron con un exceso enantiomérico del 89 y 83%, respectivamente. Tras su reducción resultaron las piperidinas **174** and **175**, que se aislaron con excesos enantioméricos del 84% y 83% ee, respectivamente (esquema 29). Concluimos, por tanto, que nuestro método de reducción no afecta de forma significativa a la integridad de los estereocentros.

21 Noole, A.; Borissova, M.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2011**, *76*, 1538.



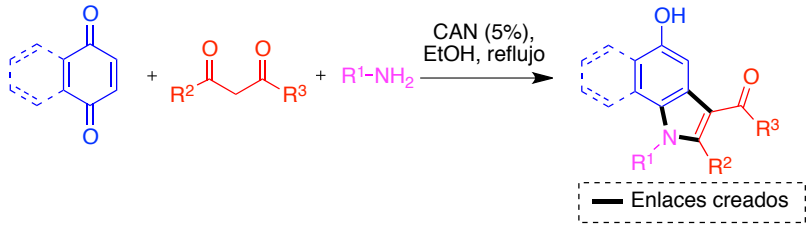

| Compuesto | R | Rto.% | ee, % |
|---|---|---|---|
| **172** | Bn | 70 | 89 |
| **173** | *n*-Pr | 62 | 83 |

| Compuesto | R | Rto., % | ee, % |
|---|---|---|---|
| **174** | Bn | 85 | 84 |
| **175** | *n*-Pr | 74 | 83 |

**Esquema 29**

## 4. CONCLUSIONES

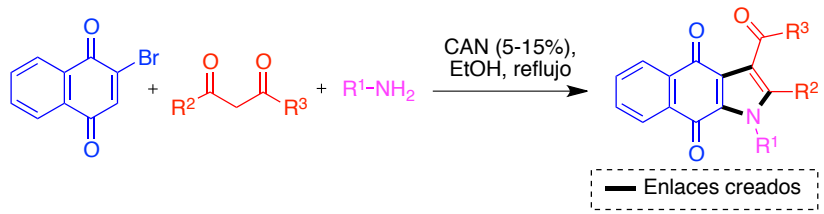
1. La reacción entre naftoquinona, compuestos β-dicarbonílicos y aminas primarias en etanol a reflujo en presencia de nitrato cérico amónico (CAN) como ácido de Lewis proporciona derivados de 5-hidroxibenzo[*g*]indol, en una versión multicomponente de la síntesis de indoles de Nenitzescu. Una reacción similar a partir de benzoquinona conduce a derivados de 5-hidroxiindol. Estas reacciones de Nenitzescu multicomponentes catalizadas por ácidos de Lewis transcurren por un mecanismo diferente de la reacción estándar.



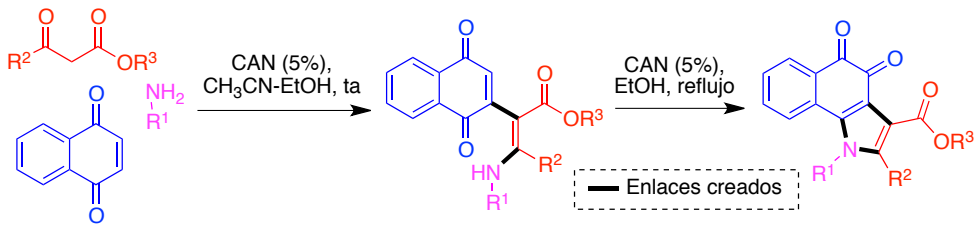

2. Productos de Nenitzescu adecuadamente sustituidos sirven de materiales de partida para reacciones de metátesis por cierre de anillo generadoras de diversidad y complejidad molecular, por aplicación del método *build-couple-pair*.


3. La sustitución de la naftoquinona por 2-bromonaftoquinona en la reacción de Nenitzescu desvía el curso de la reacción hacia un proceso

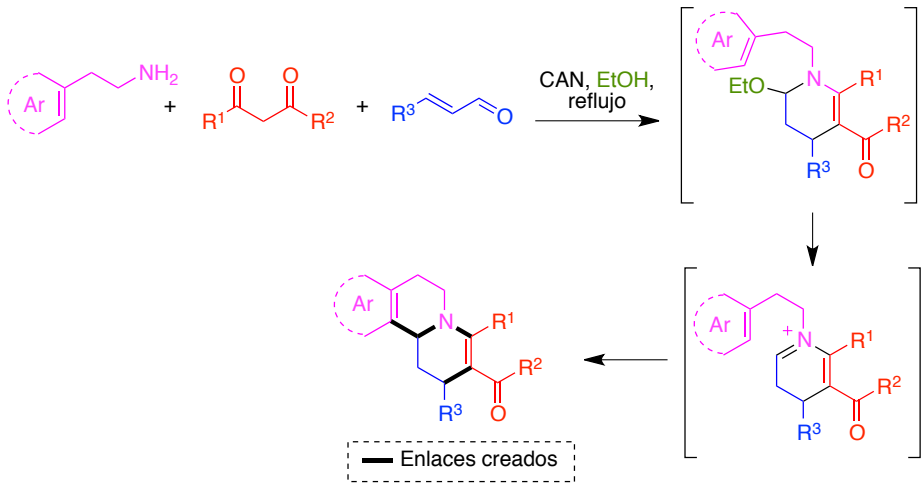
dominó de tipo Michael-Michael, que conduce sistemas lineales con estructura de benzo[*f*]indol-4,9-diona.



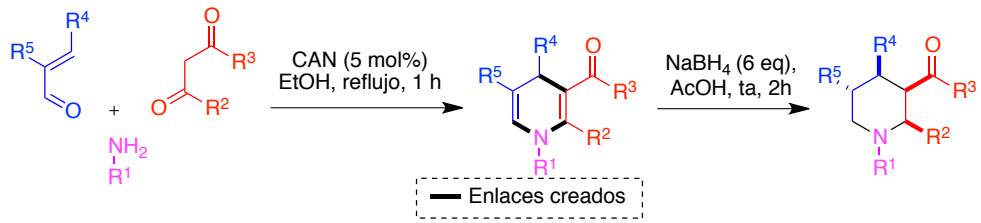

4. Una ligera modificación de las condiciones de reacción naftoquinona, compuestos β-dicarbonílicos y aminas primarias, consistente en el empleo de temperatura ambiente, permite la preparación de β-enaminonas con una molécula de quinona en posición α. Estos compuestos son materiales de partida adecuados para la obtención de *orto*-quinonas tricíclicas derivadas del sistema de benzo[*g*]indol.



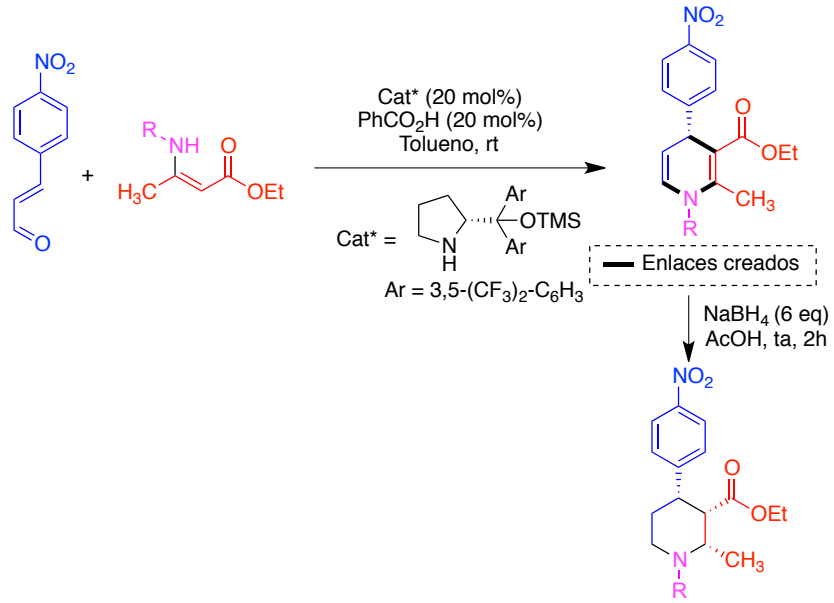

5. La combinación de una síntesis multicomponente de 6-etoxi-1,4,5,6-tetrahidropiridinas previamente desarrollada por nuestro grupo con la reacción de Pictet-Spengler condujo al desarrollo de un método diastereoselectivo de síntesis de areno[*a*]quinolizinas a partir de ariletilaminas, compuestos β-dicarbonílicos y aldehídos α,β-insaturados, que implica la generación de dos anillos, dos enlaces C-C y dos enlaces C-N en una sola operación sintética.




6. Una modificación sencilla de la reacción multicomponente previamente mencionada permite la preparación de dihidropiridinas a partir de aminas primarias, compuestos β-dicarbonílicos y aldehídos α,β-insaturados. Su reducción con triacetoxiborohidruro sódico (STAB) permitió la preparación de piperidinas polisustituidas con total diastereoselección. También fue posible la reducción de derivados de 6-etoxi-1,4,5,6-tetrahidropiridina por el mismo método.




7. Un estudio preliminar ha demostrado la posibilidad de preparar piperidinas quirales por medio de la reacción con triacetoxiborohidruro sódico.


NO2
R
NH
O
H3C
OEt
O
+
Cat* (20 mol%)
PhCO2H (20 mol%)
Tolueno, rt
Cat* =
Ar
OTMS
Ar
N
H
Ar = 3,5-(CF3)2-C6H3
NO2
O
OEt
N
R
CH3
Enlaces creados
NaBH4 (6 eq)
AcOH, ta, 2h
NO2
O
OEt
N
R
CH3

# 1. Introduction

## 1.1. MULTICOMPONENT REACTIONS AND THEIR CURRENT RELEVANCE

Modern requirements for a new synthetic method go far beyond the traditional chemo-, regio- and stereoselectivity, and can be summarized as:

1.- Ability to generate high molecular diversity and complexity.

2.- Use of simple and readily available starting materials.

3.- Experimental simplicity, leading to the possibility of automation.

4.- Low environmental impact (use of environmentally friendly solvents, atom economy, low use of energy).

The first of these requirements emerges as particularly important, and creation of molecular diversity and complexity from simple and readily available substrates is one of the major current challenges of organic synthesis.[22] The length of a synthetic route depends on the molecular complexity generated in each step and is in turn related to the number of bonds created, which can be expressed by a parameter called BFE (*Bond-*

22 Some reviews on diversity-oriented organic synthesis: (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Spring, D. R. *Org. Biomol. Chem*. **2003**, *1*, 3867. (c) Burke, M. D.; Berger, E. M.; Schreiber, M. L. *Science* **2003**, *302*, 5645. (d) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed*. **2004**, *43*, 46 (e) Tan, D. S. *Nature Chem. Biol*. **2005**, *1*, 74. (f) Wessjohann, L. A.; Ruijter, E. *Top. Curr. Chem*. **2005**, *243*, 137. (g) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem*., **2008**, *6*, 1149.

*Forming Economy*).[23] Therefore, the development of processes that allow the creation of several bonds in a single operation has become one of the more attractive goals of organic synthesis.[24] Multicomponent reactions are one of the most promising technologies towards achieving this end.

Multicomponent reactions can be defined as convergent reactions where three or more reagents are combined in such a way that the final product retains significant portions of all starting materials.[25,26,27] Ideally, they allow the simultaneous addition of all reagents, which then combine orderly

23 Dömling, A. Multicomponent Reactions-Superior Chemistry Technology for the New Millenium. *Organic Chemistry Highlights* **2005**, 5-April. http://www.organic-chemistry.org/Highlights/2005/ 05April.shtm.

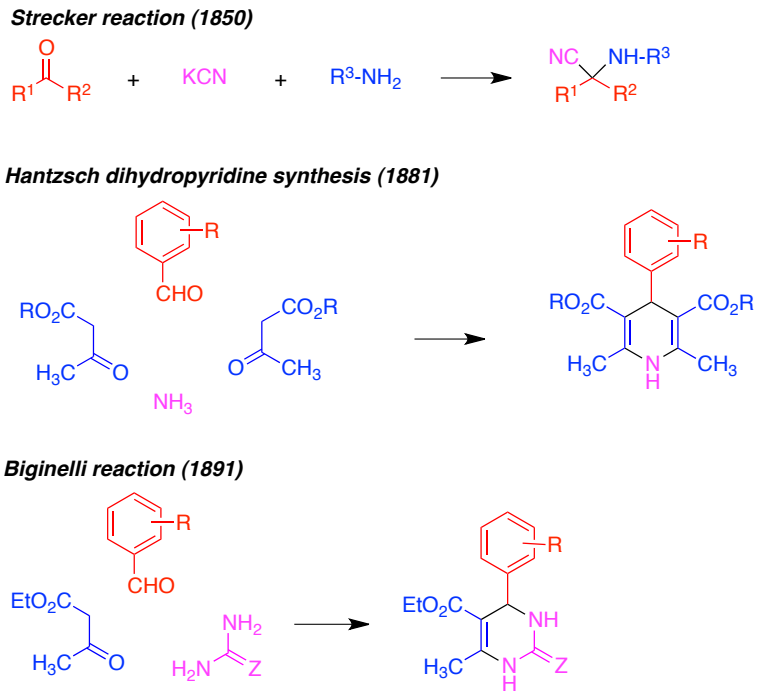
24 (a) For a review of multibond forming reactions as a pathway towards eco-compatible chemistry, see: Coquerel, Y.; Boddaert, T.; Presset, M.; Mailhol D.; Rodriguez, J.; *Ideas in Chemistry and Molecular Sciences,* in *Advances in synthetic chemistry*, ed. B. Pignataro, Wiley-VCH, Weinheim, vol. 1, chapter 9, **2010**. (b) For a Special Issue on this topic, see: Menéndez, J. C. (ed.), *Curr. Org. Chem*. **2013**, *17*, issue 18.

25 For a monograph on multicomponent reactions, see: Zhu, J.; Bienaymé, H. (eds.), Multicomponent Reactions. Wiley-VCH, **2005**.

26 Some general reviews on multicomponent reactions, with special emphasis on the use of isonitriles in (a-c, g): (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3168. (b) Ugi, A. *Pure Appl. Chem.* **2001**, *73*, 187. (c) Ugi, A. *Molecules* **2003**, *8*, 53. (d) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (e) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (f) Tejedor, D.; González-Cruz, D.; Santos-Expósito, A.; Marrero-Tellado, J. J.; de Armas, P.; García-Tellado, F. *Chem. Eur. J.* **2005**, *11*, 3502. (g) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (h) Liéby-Muller, F.; Simon, C.; Constantieux, T.; Rodriguez, J. *QSAR Comb. Sci.* **2006**, *25*, 432. (i) Guo, H.; Ma, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 354 (k) Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484. (j) Touré, B. B.; Hall, D. G. *Chem. Rev*. **2009**, *109*, 4439. (k) Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300. (l) Eckert, H.; *Molecules* **2012**, *17*, 1074. (m) Singh, M.S.; Chowdhury, S. *RSC Adv*. **2012**, *2*, 4547.

27 Reviews on asymmetric multicomponent reactions: (a) Ramón, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602. (b) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. (c) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. *Tetrahedron: Asymmetry* **2010**, *21*, 1085. (d) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. en *Targets in Heterocyclic Systems - Chemistry and Properties*, Vol. 15, Eds.: Attanasi, O. A.; Spinelli, D. Societá Chimica Italiana, Roma, **2011**, p. 140. (e) Yu, J.; Shit, F.; Gong, L. Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (f) de Graaff, C.; Ruijter E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969.

under the same reaction conditions to afford the final products. However, in order to avoid side reactions, very often it is necessary to add the reagents consecutively, and in these cases they are described as sequential multicomponent reactions. Multicomponent reactions have a long history, and indeed some of them, such as the classical Strecker, Hantzsch and Biginelli reactions were discovered during the second half of the XIX century (Scheme 1.1).

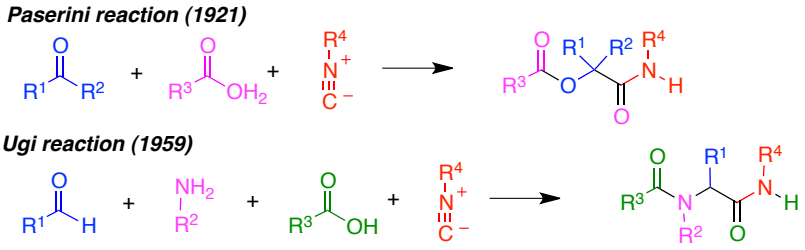



**Scheme 1.1**. The first three multicomponent reactions described in the literature

Multicomponent reactions have recently experienced an explosive growth prompted by their key role in pharmaceutical research, especially in the fields of combinatorial and diversity-oriented synthesis, since they are perfectly suited for the creation of libraries with a high degree of structural

diversity.[28] As a consequence, the development of new multicomponent reactions is a significant part of the research work currently carried out in pharmaceutical companies.[29]

The best studied multicompoment reactions are those involving the use of isonitriles as one of the components, the so-called IMCRs (*isocyanide-based multicomponent reactions*).[4a-c,g] They are particularly versatile because of the special reactivity of the isonitrile group, which bears a carbon atom that can behave as a nucleophile and an electrophile and also take part in radical reactions, confers acidity to its α protons and has affinity for many metals. Most IMCRs are focused on the construction of peptide-like structures and can be referred to two classical reactions described by Paserini and Ugi, shown in Scheme 1.2.




**Scheme 1.2**. The two classical isocyanide-based multicomponent reactions

28 Review on the impact of molecular complexity on the discovery of new lead compounds in drug research: Hann, M. M.; Leach, A. R. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 856.

29 Reviews on the applications of multicomponent reactions in drug discovery: (a) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304. (b) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085. (c) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (d) Ulaczyk-Lesanko, A.; Hall, D. G. *Curr. Opin. Chem. Biol.* **2005**, *9*, 266. (e) Slobbe, P.; Ruijter E.; Orru, R. V. A. *Med. Chem. Commun*. **2012**, *3*, 1189. (f) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev*. **2012**, *112*, 3083. (g) Ruijter E.; Orru, R. V. A. *Drug Discov. Today: Technol.* **2013**, *10*, 15-20.

Bearing in mind that more than 60% of drug molecules are heterocycles, it is surprising that multicomponent reactions leading directly to heterocyclic frameworks have not received closer attention.[30] In this context, the present thesis deals with the application of multicomponent strategies to the synthesis of functionalized polyheterocyclic frameworks, using reaction sequences that start with the formation of a β-enaminone.

30 For selected reviews of the synthesis of heterocycles using multicomponent reactions as key steps, see: (a) Sapi, J.; Laronze, J.-Y. *Arkivoc* **2004** (vii) 208. (b) D'Souza, D. M.; Mueller, T. J. J. *Chem. Soc. Rev*. **2007**, *36*, 1095. (c) Isambert, N.; Lavilla, R. *Chem. Eur. J.* **2008**, *14*, 8444. (d) Sunderhaus, J. D.; Martin, S.-F. *Chem. Eur. J*. **2009**, *15*, 1300. (e) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. *Chem. Asian J.* **2010**, *5*, 2318. For a monograph, see: Ruijter, E.;. Orru, R. V. A. *Synthesis of heterocycles via multicomponent reactions,* vols. 1 and 2*,* Springer Verlag, **2010** (*Topics in Heterocyclic Chemistry* series, volumes 23 and 25).

## 1.2. MULTICOMPONENT REACTIONS INITIATED BY THE FORMATION OF A β-ENAMINONE

β-Enaminones are important intermediates in the synthesis of many families of organic compounds[31] including β-amino acids[32] and heterocycles,[33] but their involvement as intermediates in multicomponent reactions has been relatively little studied. We will summarize below the main developments in this area, with emphasis in reactions leading to the synthesis of heterocycles.

### 1.2.1. Furan derivatives

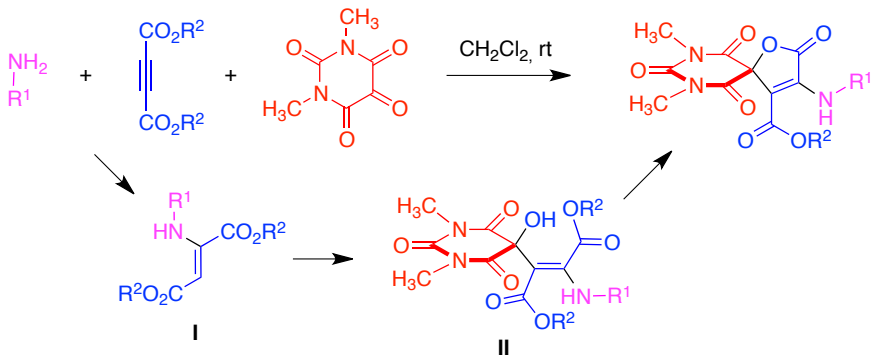
The three-component reaction between primary amines, dialkyl acetylenedicarboxylates and 1,3-dimethylalloxan affords spiro compounds containing a butenolide fragment, without the need for a catalyst. This process was proposed to be initiated by the formation of β-enaminone **I** by the aza-Michael addition of the primary amine to the dialkyl acetylenedicarboxylate component. The nucleophilic end of I would then add to the only ketone group of the alloxan, which is more electrophilic than the lactam carbonyls, leading to γ-hydroxyester **II**. Its cyclization *via* intramolecular transesterification explains the isolation of the lactone final products (Scheme 1.3).[34]

31 For a general review, see: Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463.

32 For reviews, see: (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (b) Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2101. (c) Bruneau, C.; Renaud, J.-L.; Jerphagnon, T. *Coord. Chem. Rev.* **2008**, *252*, 532.

33 For reviews, see: (a) Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1996**, *67*, 207–343. (b) Michael, J. P.; de Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem*. **1999**, *71*, 979.

34 Teimouri, M. B.; Abbasi, T. *Tetrahedron* **2010**, *66*, 3795.

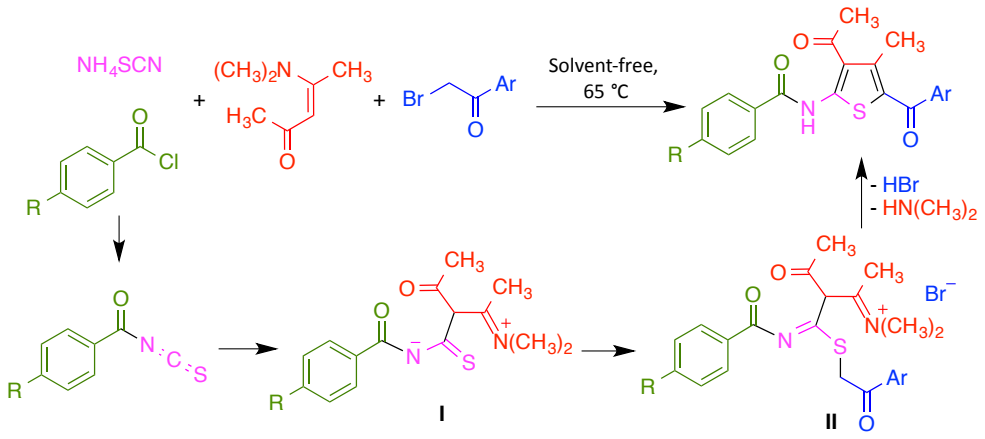



**Scheme 1.3**. Three-component synthesis of spiro butenolides

### 1.2.2. Thiophene derivatives

The four-component, one-pot reaction between ammonium thiocyanate, acyl chlorides, α-halocarbonyls and enaminones under solvent-free conditions at 65 °C was found to afford highly substituted and functionalized thiophene derivatives.[35] This complex transformation was proposed to take place by the mechanism summarized in Scheme 1.4, which involves the initial reaction between ammonium thiocyanate and the acyl chloride to furnish an isothiocyanate. Its subsequent reaction with the β-enaminone would afford intermediate **I**, which would then react with the phenacyl bromide to give **II**. Its cyclization by attack of the methylene that is α simultaneously to the S atom and the ketone carbonyl onto the iminium group, followed by elimination of dimethylamine, leads to the final product.

35 Hossaini, Z.; Rostami-Charati, F.; Soltani, S.; Mirzaei, A.; Berijani, K. *Mol. Divers*. **2011**, *15*, 911.



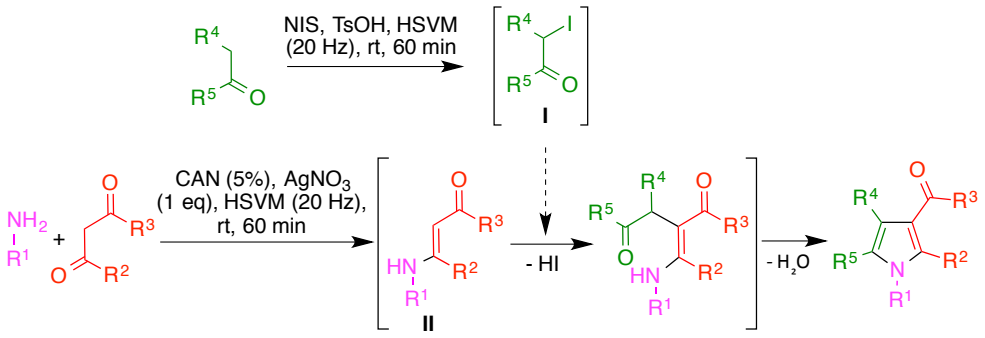

**Scheme 1.4**. Four-component synthesis of thiophene derivatives

### 1.2.3. Pyrrole derivatives

The original version of the Hantzsch pyrrole synthesis involved the reaction between ethyl β-aminocrotonate and phenacyl chloride. Although some three-component versions have been published, particularly those based on the use of solid-phase[36] and flow[37] chemistries, they lack generality and normally give low yields. In this context, our group has recently reported a sequential multicomponent process involving the high-speed vibration milling of ketones with *N*-iodosuccinimide and *p*-toluenesulfonic acid, followed by addition of a mixture of primary amines, β-dicarbonyl compounds, cerium(IV) ammonium nitrate and silver nitrate that affords polysubstituted, functionalized pirroles in good to excellent yields (Scheme 1.5). This one-pot, solid-state process can be viewed as the coupling of an α-iodoketone preparation with a generalized version of the classical Hantzsch pyrrole synthesis. Furthermore, it is the first multicomponent reaction carried out under high-speed vibration milling conditions with the

36 Trautwein, A. W.; Süssmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381.
37 Herath, A.; Cosford, N. D. P. *Org. Lett*. **2010**, *12*, 5182.

sole input of mechanical energy.[38]




**Scheme 1.5**. Mechanochemical synthesis of pirroles based on the Hantzsch reaction

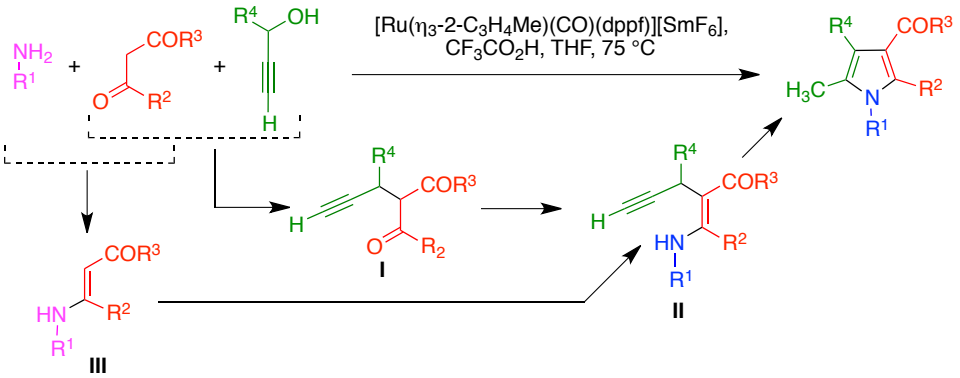
A one-pot, three-component reaction between primary amines, β-ketoesters or β-diketones and propargyl alcohols provided an efficient entry into pyrroles, as shown by Gimeno and coworkers.[39] This transformation was carried out in sealed vessels using tetrahydrofuran containing trifluoroacetic acid as the reaction medium and in the presence of the [Ru($\eta_3$-2-$C_3H_4$Me)(CO)(dppf)][$SbF_5$] system, where dppf is 1,1'-bis(diphenylphosphanyl)ferrocene, and afforded fully substituted derivatives of the pyrrole system in good to excellent yields.[40] Mechanistically, this transformation was explained by two competitive pathways. In the first one, an acid-promoted propargylation of the β-dicarbonyl substrate affords a γ-ketoalkyne **I**, which could be isolated in a separate experiment. This intermediate then reacts with the primary amine

38 Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Commun*. **2013**, *49*, 591.

39 Cadierno, V.; Gimeno, J.; Nebra, N. *Chem. Eur. J.* **2007**, *13*, 9973.

40 Subsequent work by a different group proved that the synthesis of pyrroles from primary amines, β-dicarbonyl compounds and propargyl alcohols can be carried out under experimentally simpler conditions, using indium trichloride as catalyst and toluene as solvent: Lui, X.-T.; Huang, L.; Zheng, F.-J.; Zhan, Z. P. *Adv. Synth. Catal.* **2008**, *350*, 2778.

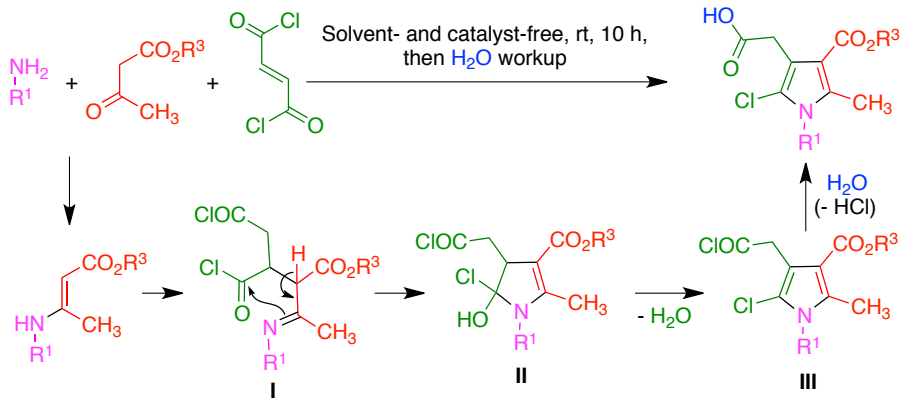
to give the propargylated β-enaminone **II**, which undergoes a final Ru-catalyzed 5-*exo-dig* annulation leading to the observed pyrrole final products. Alternatively, intermediate **II** can be reached by propargylation of β-enaminone **III**, which was detected by GC-MS experiments. These proposals are summarized in Scheme 1.6.




**Scheme 1.6**. Ru-catalyzed synthesis of pyrroles by the three-component reaction between primary amines, β-dicarbonyl compounds and propargyl alcohols

A solvent- and catalyst-free synthesis of pentasubstituted, functionalized pyrrole systems has been developed recently, based on the three-component reaction between primary amines, alkyl acetoacetates and fumaryl chloride. The pyrrole derivatives thus obtained contain a 5-chloro substituent, together with carboxylic ester and carboxymethyl functional groups. The proposed mechanism starts by the formation of a β-enaminone, followed by its Michael addition to a molecule of fumaryl chloride to afford **I**. The intramolecular attack of the enamine nitrogen onto the acyl chloride function leading to the generation of the five-membered ring did not follow the expected pathway with elimination of

HCl, but instead involved the loss of a molecule of water with retention of the chlorine substituent (Scheme 1.7).[41]




**Scheme 1.7**. Three-component reaction between primary amines, alkyl acetoacetates and fumaryl chloride.

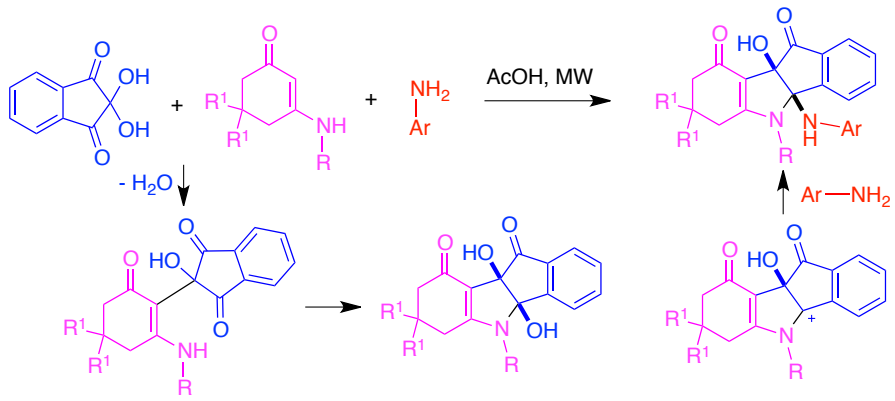
### 1.2.5. Indole derivatives

The microwave-promoted reaction between ninhydrin, cyclic β-enaminones and aromatic amines in acetic acid afforded tetracyclic indeno[1,2-*b*]indole derivatives in diastereoselective fashion, through the mechanism summarized in Scheme 1.8.[42] By replacing ninhydrin by arylglyoxal hidrates, the reaction could be adapted to the preparation of 2-arylindoles.[43]

41 Alizadeh, A.; Babaki, M.; Zohreh, N. *Tetrahedron* **2009**, *65*, 1704.

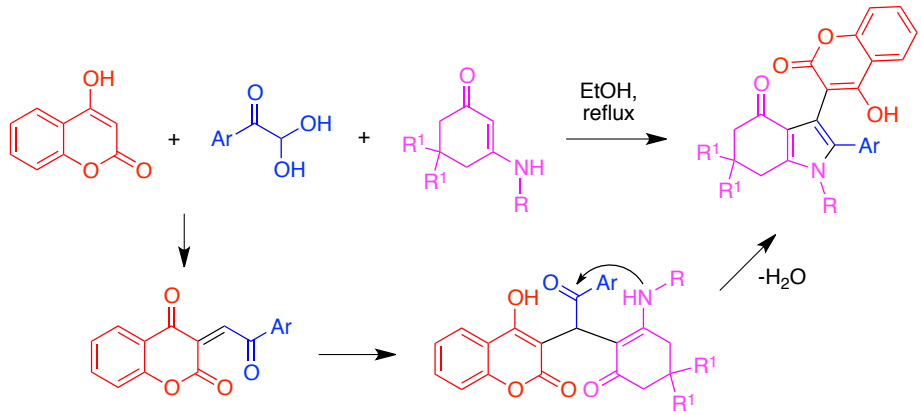
42 Jiang, B.; Li, Q.-Y.; Tu, S.-J.; Li, G. *Org. Lett*. **2012**, *14*, 5210.

43 (a) Jiang, B.; Tu, M.-S.; Wang, S.-L.; Tu, S.-J.; Li, G. *ACS Comb. Sci*. **2012**, *77*, 7497. (b) Fu, L.-P.; Shi, Q.-Q.; Shi, Y.; Jiang, B.; Tu, S.-J. *ACS Comb. Sci*. **2013**, *78*, 135.



**Scheme 1.8**. Three-component synthesis of indeno[1,2-*b*]indole derivatives

In a related transformation, functionalized dihydroindol-4(5*H*)-ones were prepared by a catalyst-free, three-component reaction of 1,3-dicarbonyl compounds, arylglyoxal monohydrate and enaminones in refluxing ethanol (Scheme 1.9).[44] Interestingly, pure products were obtained by washing the reaction products with ethanol, avoiding the need for chromatography or recrystallization.

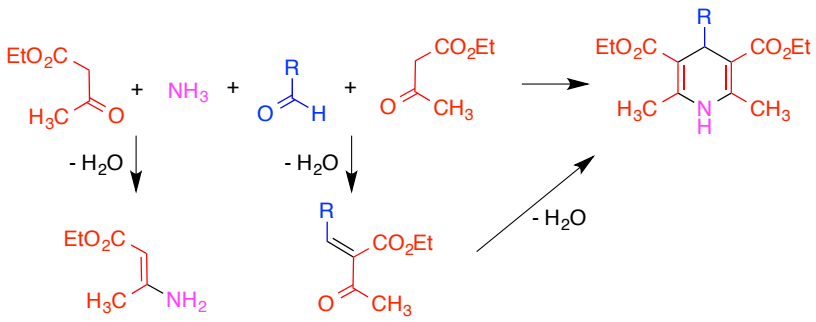


**Scheme 1.9**. Three-component synthesis of dihydro-1*H*-indol-4(5*H*)-ones

44 Wang, H.-Y.; Shi, D.-Q. *ACS Comb. Sci*. **2013**, *78*, 261.

### 1.2.6. Pyridine derivatives

The traditional Hantzsch dihydropyridine synthesis, involving the reaction between β-dicarbonyl compounds, aldehydes and ammonia, proceeds via a β-enaminone intermediate (Scheme 1.10).




**Scheme 1.10**. The Hantzsch dihydropyridine synthesis

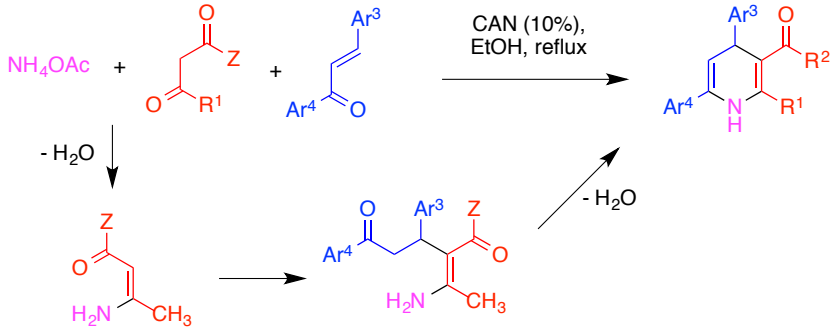
Our group has developed some enaminone-initiated dihydropyridine syntheses catalyzed by cerium(IV) ammonium nitrate (CAN)[45] that are complementary in their scope to the traditional Hantzsch method. In one of them, the reaction between chalcones, β-dicarbonyl compounds and ammonium acetate afforded 5-unsubstituted 4,6-diaryldihydropyridines, which were designed *not* to satisfy the well-known structure-activity relationships for cardiovascular activity in dihydropyridines and thus be suitable candidates as neuroprotectors by regulation of the intracellular calcium levels in neurons (Scheme 1.11).[46] Some variations were found for this reaction, and thus the use of β-ketoamides was found lo lead directly to pyridine derivatives related to nicotinamide.[47] Interestingly, when the

45 For a review of the use of CAN as a catalyst in synthesis, see: Sridharan, V.; Menéndez, J. C. *Chem. Rev.*, **2010**, *110*, 3805.

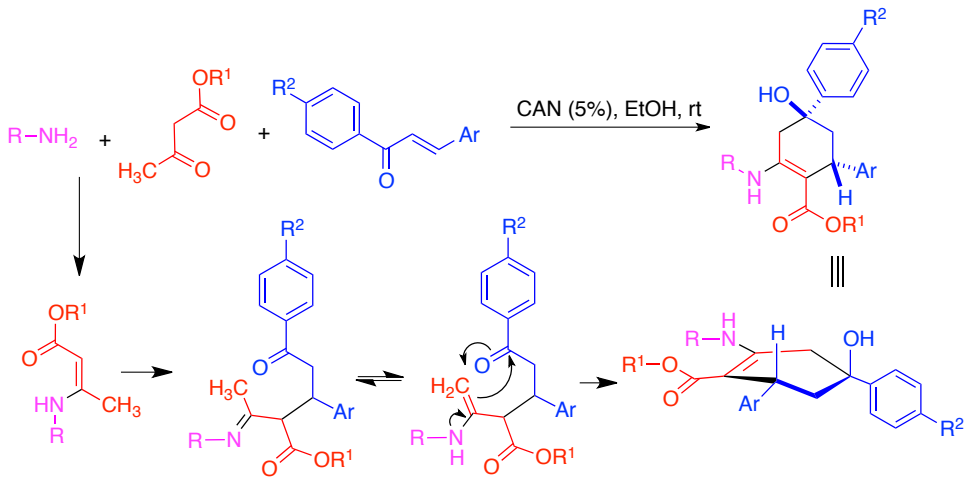
46 Tenti, G.; León, R.; Egea, J.; Villarroya, M.; Fernández, J. C.; Padín, J. F.; Sridharan, V.; Ramos, M. T.; Menéndez, J. C. *Med. Chem. Commun*. **2013**, *4*, 590.

47 Tenti, G.; Ramos, M. T.; Menéndez, J. C. *ACS Comb. Sci.* **2012**, *14*, 551.

ammonium salt was replaced by a primary amine the reaction took a completely different course, affording polysubstituted cyclohexene derivatives having a β-aminoester moiety (Scheme 1.12).[48]




**Scheme 1.11**. Three-component synthesis of 4,6-diaryl-1,4-dihydropyridines from chalcones, β-dicarbonyl compounds and ammonium acetate

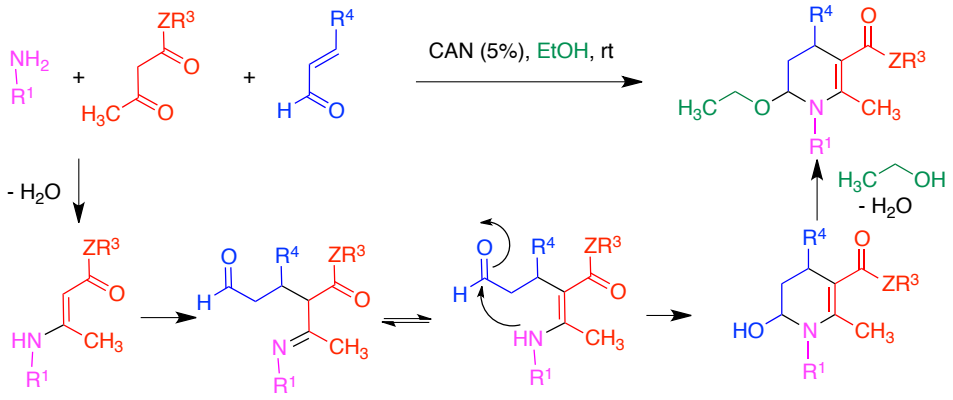



**Scheme 1.12**. Three-component synthesis of cyclic β-aminoesters from chalcones, β-dicarbonyl compounds and primary amines

Finally, replacement of the chalcone component by an α,β-unsaturated aldehyde led to yet another reaction mode, affording 1-alkyl-6-alkoxy-

48 (a) Sridharan, V.; Menéndez, J. C. *Org. Lett.* **2008**, *10*, 4303. (b) Rocchi, D.; González, J. F.; Menéndez, J. C. *Green Chem*. **2013**, *15*, 511.

1,4,5,6-tetrahydropyridine derivatives (Scheme 1.13).[49] The transformation of these compounds into the corresponding dihydropyridines, together with some synthetic applications of the latter, was also investigated.[50]




**Scheme 1.13**. Four-component synthesis of 6-alkoxy-1,4,5,6-tetrahydropyridines from acroleins, β-dicarbonyl compounds, primary amines and alcohols

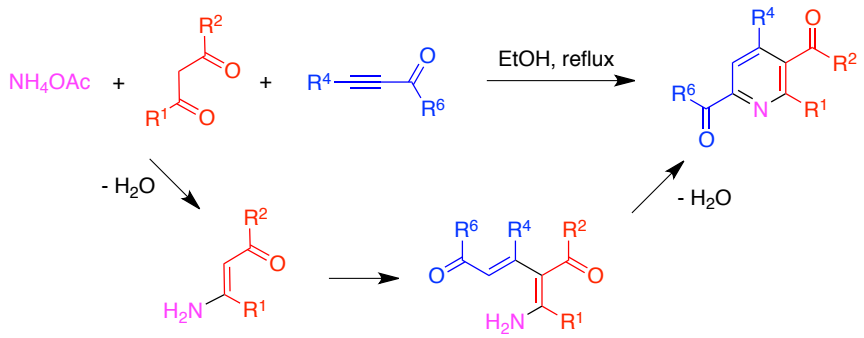
The Bohlmann-Rahtz pyridine synthesis was first initially based on the reaction between ethyl β-aminocrotonate or related enamines and ethynyl ketones or aldehydes.[51] In order to overcome limitations associated to the low stability of the starting enaminones, it was later developed as a three-component reaction of a β-ketoester, an alkynone and a source of ammonia. The enaminone is generated *in situ* and then reacts with the alkynone to give an aminodienone intermediate that undergoes spontaneous acid-catalyzed cyclodehydration to give the pyridine product (Scheme 1.14). Initially, AcOH and $ZnBr_2$ were used as acid catalysts with toluene as solvent, but it was later shown that acid-sensitive substrates could also be employed by carrying out the reaction under acid-free

49 (a) Sridharan, V.; Maiti, S.; Menéndez, J. C. *Chem. Eur. J.* **2009**, *15*, 4565. (b) Sridharan, V.; Maiti, S.; Menéndez, J. C. *J. Org. Chem*. **2009**, *74*, 9365.

50 (a) Maiti, S.; Menéndez, J. *Synlett* **2009**, 2249. (b) Maiti, S.; Sridharan, V.; Menéndez, J. C. *J. Comb. Chem.* **2010**, *12*, 713.

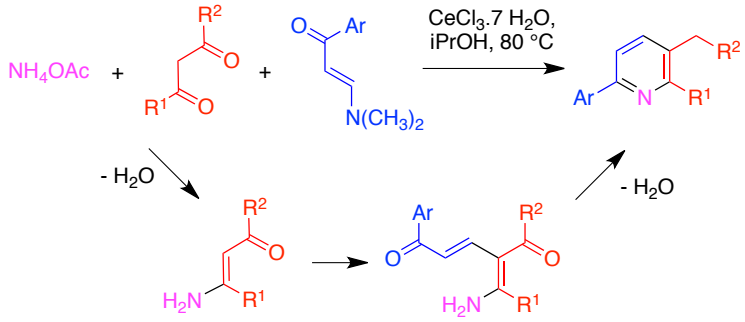
51 For a review, see: Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459.

conditions, by simply refluxing the starting materials in ethanol.[52]




**Scheme 1.14**. The three-component Bohlmann-Rahtz pyridine synthesis

In a related method, *N*,*N*-dimethyl-β-enaminones obtained from aryl or heteroaryl methyl ketones were treated with ethyl acetoacetate and ammonium acetate in refluxing in 2-propanol containing $CeCl_3.7H_2O$-NaI as a catalyst, to give pyridine derivatives though a mechanism similar to the one described for the Bohlmann-Rahtz reaction (Scheme 1.15).[53]

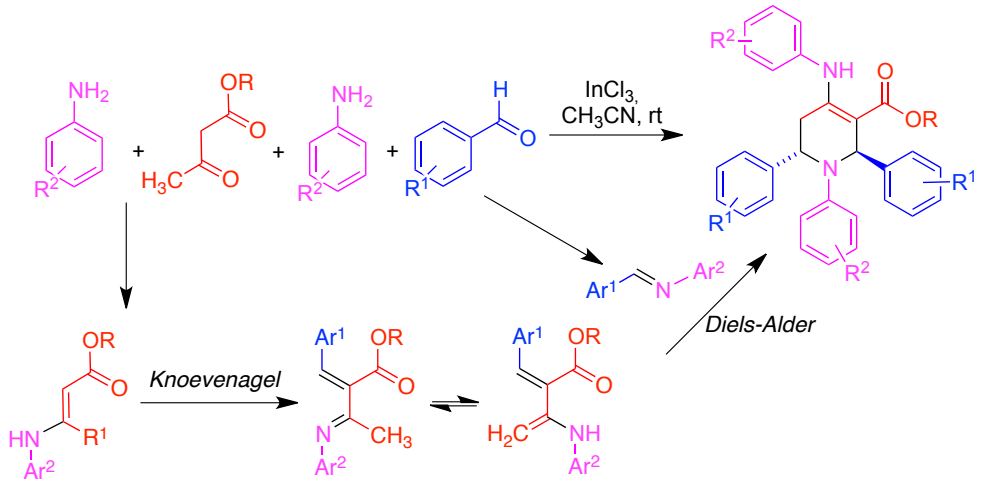



**Scheme 1.15**. A three-component variation of the Bohlmann-Rahtz pyridine synthesis

52 Xiong, X.; Bagley, M. C.; Chapaneri, K. *Tetrahedron Lett*. **2004**, *45*, 6121.

53 Kantevari, S.; Patpi, S. R.; Addla, D.; Putapatri, S. R.; Sridhar, B.; Yogeeswari, P.; Sriram, D. *ACS Comb. Sci.* **2011**, *13*, 427.

Another CAN-catalyzed tetrahydropyridine synthesis *via* a multicomponent reaction between anilines, β-ketoesters and aromatic aldehydes, whose authors describe as "Pot, Atom and Step Economic" (PASE), and is summarized in Scheme 1.16.[54] This process was proposed to start by the formation of a β-enaminone from the dicarbonyl compound and one molecule of aromatic amine. A Knoevenagel-type reaction between this intermediate and a molecule of aldehyde followed by double bond isomerization would give a 2-aminobutadiene. Its aza Diels-Alder reaction with a molecule of the imine arising from the aldehyde and a second molecule of aniline would explain the isolation of the final product.




**Scheme 1.16**. Five-component synthesis of 1,2,5,6-tetrahydropyridines

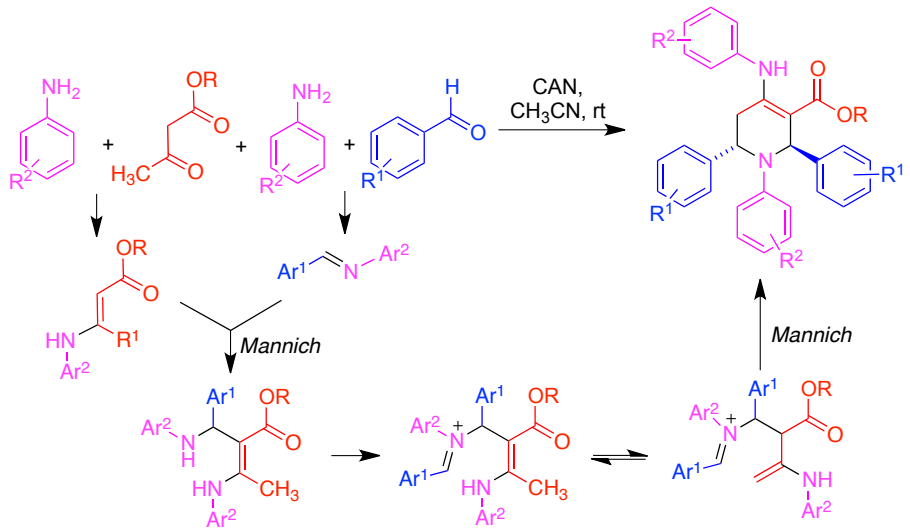
An alternative mechanism has been proposed by subsequent authors that have described the use of CAN[55] or boron trifluoride[56] as a catalyst for this reaction, which involves a Mannich reaction between the enamine and

54 Clarke, P. A.; Zaytsev, A. V.; Whitwood, A. C. *Tetrahedron Lett*. **2007**, *48*, 5209. (b) Clarke, P. A.; Ermanis, K. *Curr. Org. Chem*. **2013**, *17*, 2025.

55 Wang, H.-J.; Mo, L.-P.; Zhang, Z. H. *ACS Comb. Sci*. **2011**, *13*, 181.

56 Ramachandran, R.; Jayanthi, S.; Jeong, Y. T. *Tetrahedron* **2012**, *68*, 363.

imine intermediates, followed by reaction of the nitrogen atom with a second molecule of aldehyde to give an iminium species, which would cyclize *via* double bond isomerization and a final intramolecular Mannich cyclization (Scheme 1.17).

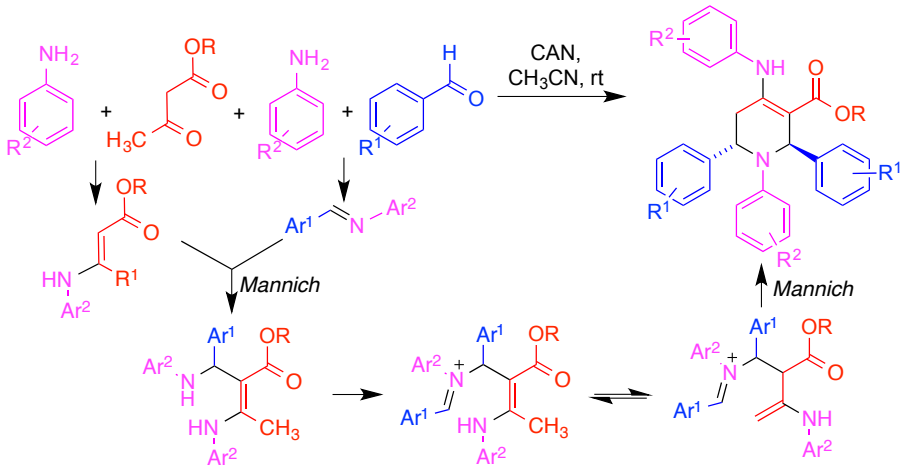



**Scheme 1.17**. Alternative mechanism proposed to explain the five-component tetrahydropyridine synthesis

### 1.2.7. Pyrimidine derivatives

The four-component reaction between aromatic aldehydes, N,N-dimethyl enaminones, aromatic amines, and thiourea in the presence of a co-catalyst of TMSCl/CAN bicatalytic system afforded tetrahydro-pyrimidinethiones bearing three adjacent stereocenters with complete diastereoselectivity.[57] This transformation may be explained by the mechanism summarized in Scheme 1.18, comprising an amine exchange, a Knoevenagel reaction to give a 1-azadiene, a Michael addition of thiourea and a final 6-*exo*-*trig* cyclization.

57 Wan, J.-P.; Wang, C.; Pan, Y. *Tetrahedron* **2011**, *67*, 922.



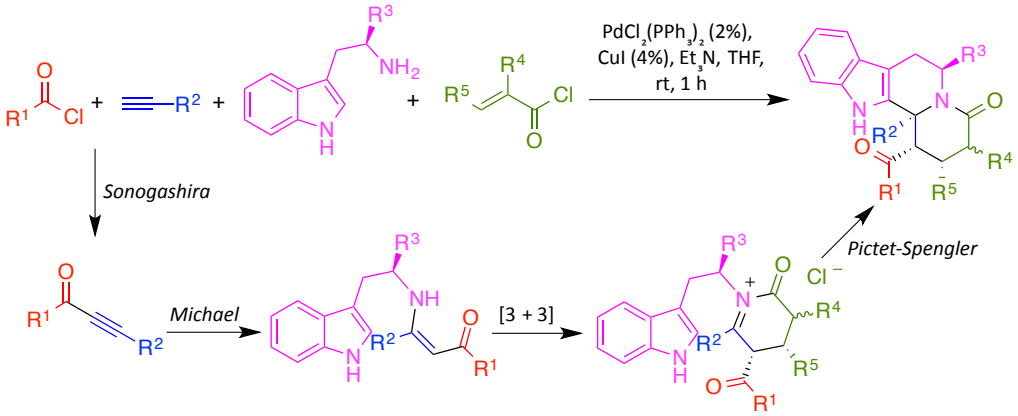

**Scheme 1.18**. Four-component synthesis of tetrahydropyrimidinethiones

### 1.2.8. Polyheterocyclic systems

The Müller group has studied a variety of sequential and consecutive transformations initiated by the formation of alkynones by Sonogashira coupling of acid chlorides and terminal alkynes.[58] In the course of this work, they have investigated the consecutive four-component reaction of acid chlorides, alkynes, tryptamine derivatives and α,β-unsaturated acid chlorides to give indolo[2,3-*a*]quinolizidines in a single synthetic operation. This complex process was proposed to be initiated by a Sonogashira coupling between the acyl chloride and the terminal alkyne to give an ynone. Its reaction with the tryptamine affords a β-enaminone, which reacts with the α,β-unsaturated acyl chloride in a formal [3+3] cycloaddition that takes place *via* a cationic aza-Cope rearrangement having a chair-like transition state that explains the *syn* orientation of the $R^6$ and carbonyl substituents. Finally, the resulting acyliminium species is cyclized to the final product in a Pictet-Spengler reaction (Scheme 1.19).[59]

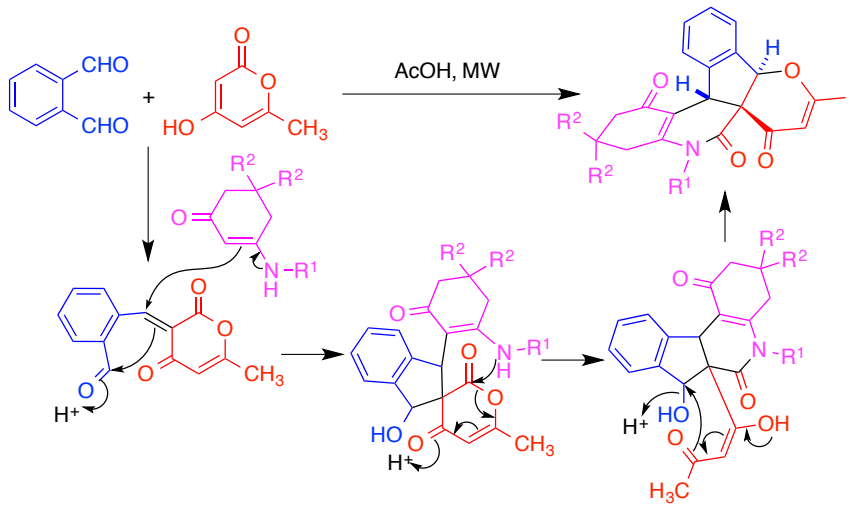
58 For a review, see: Willy, B.; Müller, T. J. J. *Arkivoc* **2008** (i) 195.

59 (a) Karpov, A. S.; Oeser, T.; Müller, T. J. J. *Chem. Commun*. **2004**, 1502. (b) Karpov, A. S.; Rominger, F.; Müller, T. J. J. *Org. Biomol. Chem*. **2005**, *3*, 4382.




**Scheme 1.19**. Four-component synthesis of indolo[2,3-*a*]quinolizidines

Li has described the preparation of complex pentacyclic systems containing an indeno[2,1-c]quinoline core by treatment of *o*-phthalaldehyde with 4-hydroxy-6-methyl-2*H*-pyran-2-one and cyclic enaminones.[60] The domino process summarized in Scheme 1.20 was proposed to explain this transformation.



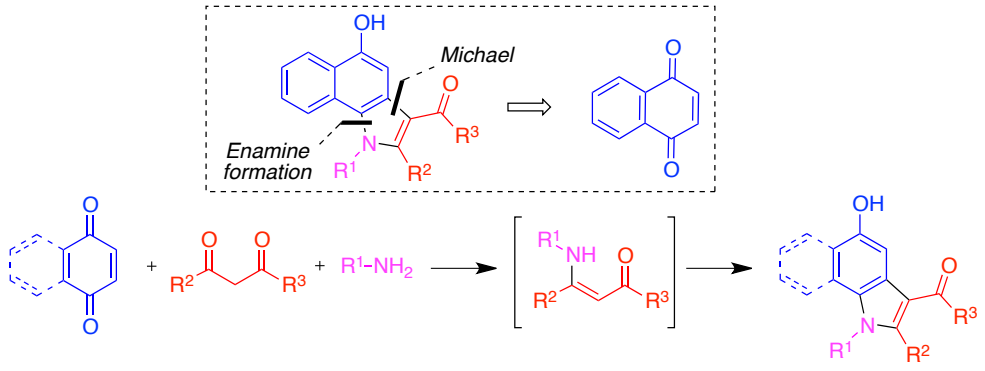

**Scheme 1.20**. Multicomponent synthesis of pentacyclic compounds derived from the indeno[2,1-*c*]quinoline system

60 Jiang, B.; Feng, B.-M.; Wang, S.-L.; Tu, S.-J.; Li, G. *Chem. Eur. J.* **2012**, *18*, 9823.

# 2. Objectives

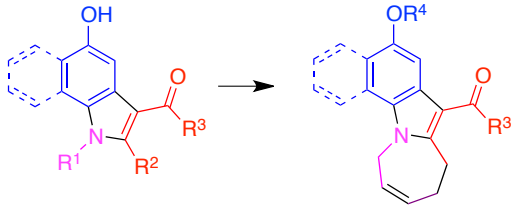
In the context of the development of multicomponent reactions initiated by the formation of a β-enaminone for the synthesis of heterocycles with potential pharmacological interest, the present thesis has the following specific objectives:

1.- Development of a multicomponent, general version of the Nenitzescu indole synthesis (Scheme 2.1).



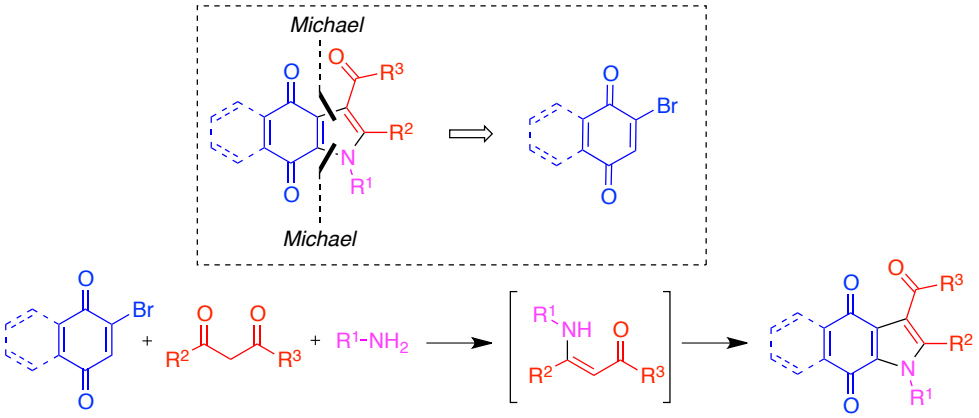

**Scheme 2.1**

2. Use of the Nenitzescu products as starting materials for complexity-generating reactions as an application of the build-couple-pair approach to the generation of molecular diversity (Scheme 2.2).



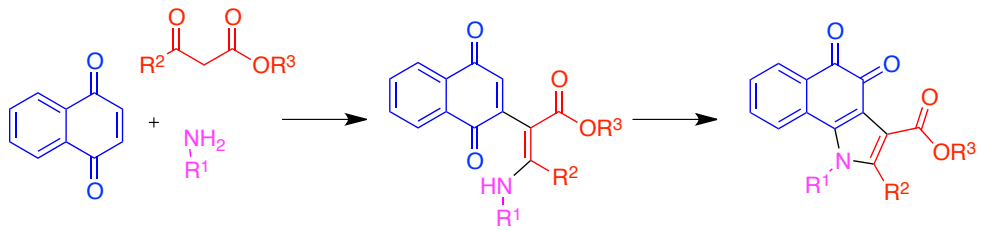

**Scheme 2.2**

3. Development of a variation of the Nenitzescu reaction that allows the synthesis of indolequinones by adding a leaving group to the quinone starting material (Scheme 2.3).



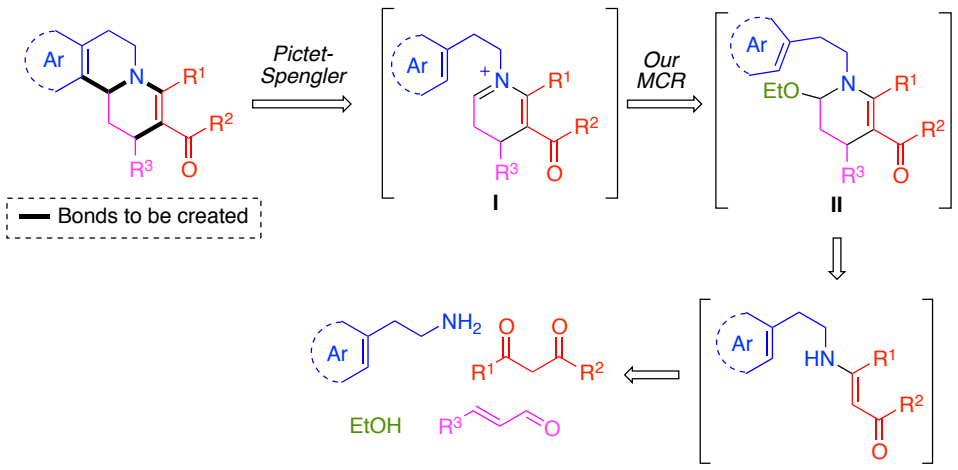

**Scheme 2.3**

4. Development of a three-component method for the synthesis of β-enaminones coupled to naphthoquinone and their transformation into *ortho*-quinones derived from the benzo[*g*]indole system (Scheme 2.4).



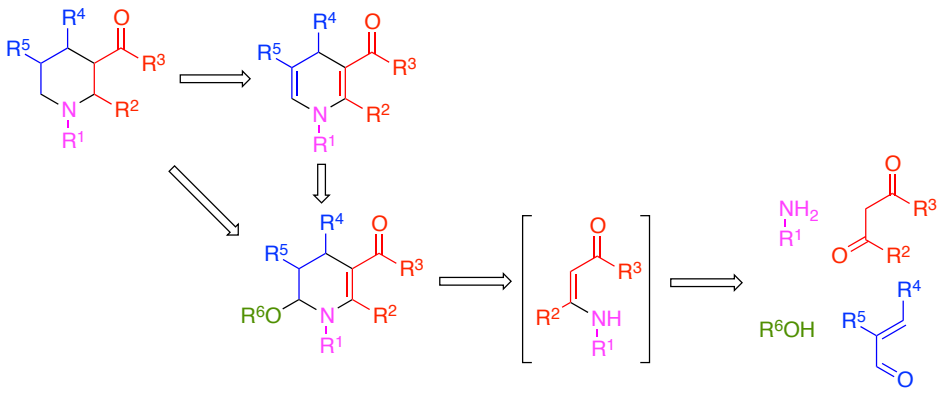
**Scheme 2.4**

5. Development of a one-pot synthesis of areno[*a*]quinolizines based on the combination of a multicomponent synthesis of 6-ethoxy-1,4,5,6-tetrahydropyridines previously developed by our group (see Scheme 1.13) with the Pictet-Spengler reaction (Scheme 2.5).




**Scheme 2.5**

6. Application of the above-mentioned multicomponent synthesis of 6-ethoxy-1,4,5,6-tetrahydropyridines to the preparation of polysubstituted piperidine derivatives, either directly or *via* its previous adaptation to the preparation of 1,4-dihydropyridines (Scheme 2.6).



**Scheme 2.6**

# 3. A generalized, multicomponent version of the Nenitzescu indole synthesis

## 3.1. INTRODUCTION

The indole ring system is a widespread structural motif in natural products (for selected examples, see Figure 3.1).[61] Many indole derivatives show therapeutically interesting biological activities,[62] and indole undoubtedly belongs to the "privileged scaffolds" category[63,64] according to the definition proposed by Evans: "A molecular framework able to provide ligands for diverse receptors". Therefore the search for new methods for

61 For selected reviews and monographs on natural indoles, see: (a) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep*., **2005**, *22*, 761. (b) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.,* **2007**, *24*, 843. (c) d'Ischia, M.; Napolitano, A.; Pezzella, A. in *Comprehensive Heterocyclic Chemistry*, ed. Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. Elsevier, Oxford, **2008,** Vol. *3*, Chapter 3.04. (d) Ishikura, M.; Yamada, K. *Nat. Prod. Rep*., **2009**, *26*, 803. (e) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.,* **2009**, *109*, 3080.

62 For selected reviews and accounts dealing with the biological importance of indoles, see: (a) Pindur, U.; Lemster, T. *Curr. Med. Chem.,* **2001**, *8*, 1681. (b) Suzen, S. Top. *Heterocycl. Chem.,* **2007**, *11*, 145. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed*., **2007**, *46*, 8748. (d) Kutschy, P.; Mexencev, R. *Targets in Heterocyclic Systems,* **2008**, *12*, 120. (e) Weng, J. R.; Tsai, C. H.; Kulp, S. K. *Chem. Cancer Lett.,* **2008**, *262*, 153. (f) Manera, C.; Tuccinardi, T.; Martinelli, A. *Mini-Rev. Med.* Chem*.,* **2008**, *8*, 370. (g) De Sa Alves, F. R.; Barreiro, E. J.; Fraga, C. A. M. *Mini-Rev. Med. Chem.* **2009**, *9*, 782. (h) Xu, H.; Lu, M. *Curr. Pharm. Des.,* **2009**, *15*, 2120. (i) Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem.,* **2009**, *16*, 2531. (j) Sarkar, F. H.; Li, Y. *Cancer Treat. Rev.,* **2009**, *35*, 597. (k) Steffan, N.; Grundmann, A.; Yin, W. B.; Kremer, A.; Li, S. M. *Curr. Med. Chem.,* **2009**, *16*, 218.

63 For the applications of the "privileged scaffold" concept in drug discovery, see: (a) Muller, G. *Drug Discovery Today*, **2003**, *8*, 681. (b) Costantino, L.; Barlocco, D. *Curr. Med. Chem.,* **2006**, *13*, 65. (c) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol*. **2010**, *14*, 1.

64 Alves, F. R. S.; Barreiro, E. J.; Fraga, C. A. M. *Mini-Rev. Med. Chem.,* **2009**, *9*, 782.

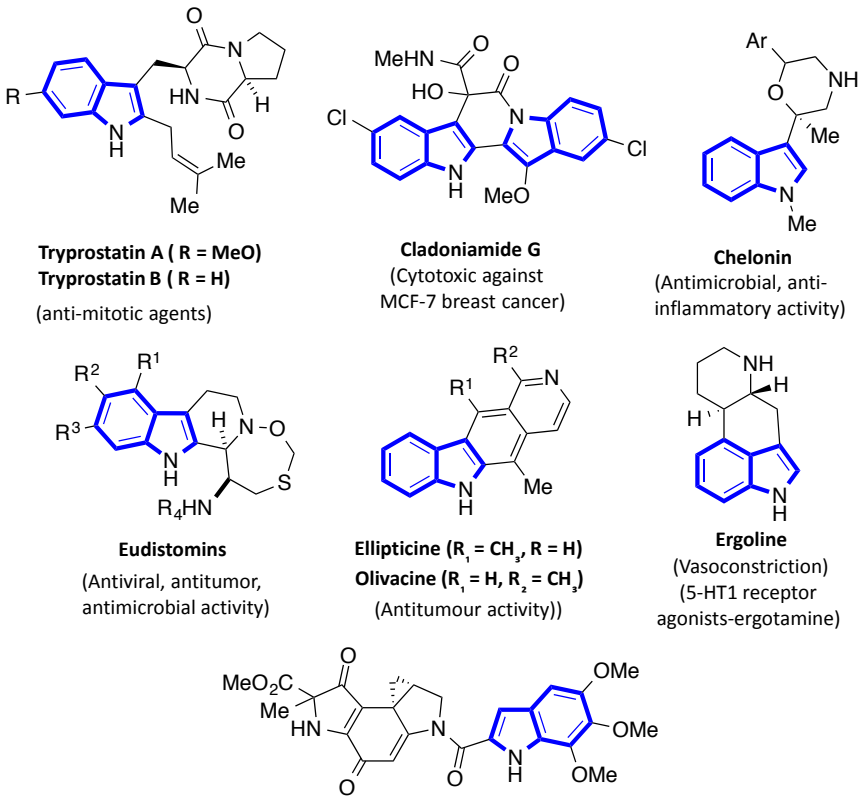



**Figure 3.1.** Some alkaloids containing indole ring systems

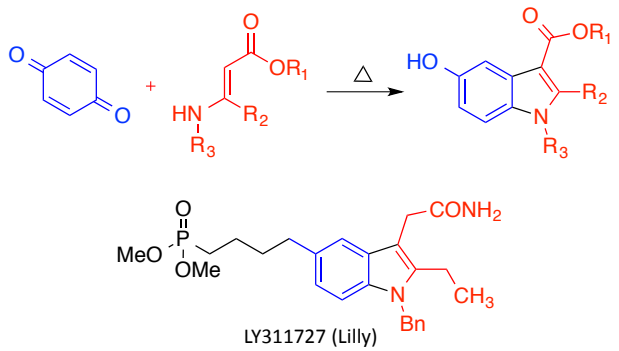
indole synthesis, together with the improvement of known procedures, is still a topical and challenging area of organic synthesis.

There is a huge array of methods for the synthesis of indoles,[65] including traditional name reactions such as the Fisher, Bischler, Reissert, Madelung, Bartoli and Saegusa reactions. More recently, organometallic reagents, specially palladium catalysts, have found widespread application for indole synthesis, leading to a number of methods that include the Buchwald,

65 For selected reviews of indole synthesis, see: (a) *Indoles*, ed. Sundberg, R. J. Academic Press: London, **1996**. (b) Sundberg, R. J. in *Comprehensive Heterocyclic Chemistry II,* ed. Katritzky, A. R.; Press, C. W.; Scriven, E. F. V.; Bird, C. W. Pergamon Press, Oxford, **1996**, Vol. *2*, p 119. (c) Gribble, G. W. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 1045. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.,* **2006,** *106*, 2875. (e) Candeias, N. R.; Branco, L. C.; Gois, P. M. P.; Afonso, C. A. M.; Trindade, A. F. *Chem. Rev.,* **2009**, *109*, 2703.

Hegedus-Mori-Heck, Larock and Yamanaka-Sakamoto indole syntheses,[66] and the C-H activation concept has also been widely applied to this problem.[67]

Among the synthetic methodologies leading to indoles, the Nenitzescu reaction[68] between 1,4-benzoquinones and β-enaminones is particularly suitable for the preparation of 5-hydroxyindoles. In comparison with other methods, it is relatively unexplored despite its experimental simplicity and the pharmaceutical applications of some products derived from it such as LY311727, a selective inhibitor of human non pancreatic secretory phospholipase A2[69] (Scheme 3.1). The main drawbacks of this method are associated to problems during the purification of the acid-sensitive enaminones and the poor yields normally obtained.




LY311727 (Lilly)

**Scheme 3.1**. The Nenitzescu reaction and an example of a bioactive molecule obtained by this method

66 For the synthesis and functionalization of indoles via palladium-catalyzed reactions, see: Cacchi, S.; Fabrizi, G. *Chem. Rev.,* **2005**, *105*, 2873.

67 For a review, see: Song, J. J.; Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Arkivoc* **2010** *(i)*, 390.

68 For selected examples and a review of the Nenitzescu reaction, see: (a) Pawlak, J. M.; Khau, V. V.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.,* **1996**, *61*, 9055. (b) Ketcha, D. M.; Wilson, L. J.; Portlock, D. E. *Tetrahedron Lett.,* **2000**, *41*, 6253. (c) Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Org. Chem.,* **2008**, *12*, 691.

69 Schevitz, R. W.; Bach, N. J.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Dillard, R. D.; Draheim, S. E.; Hartley, L. W.; Jones, N. D.; Mihelich, E. D. *Nat. Struct. Biol.,* **1995**, *2*, 458.

## 3.2 SYNTHESIS OF ANGULARLY FUSED INDOLES BY MULTICOMPONENT NENITZESCU REACTIONS: PREPARATION OF 5-HYDROXYBENZO[*g*]INDOLE DERIVATIVES

As previously mentioned, our first goal was to overcome the problems associated with the standard Nenitzescu reactions and to extend its range of synthetic applications. Since the main difficulty lies in the purification of the enaminones, the best solution would be to carry out Nenitzescu reaction in one-pot multicomponent fashion. To this end, ideally we needed to find a catalyst able to promote all steps of the process, namely the formation of the β-enaminone, its subsequent Michael addition to the quinone substrate and the final cyclocondensation. Our initial choice was cerium (IV) ammonium nitrate (CAN)[70] because of its low cost and toxicity and tolerance to moisture, and specially because our group had some experience with its use as a Lewis acid,[71] having found it to be an excellent catalyst for the formation of β-enaminones from 1,3-dicarbonyl compounds and primary amines, as mentioned in Chapter 1.[72]

### 3.2.1. Optimization studies

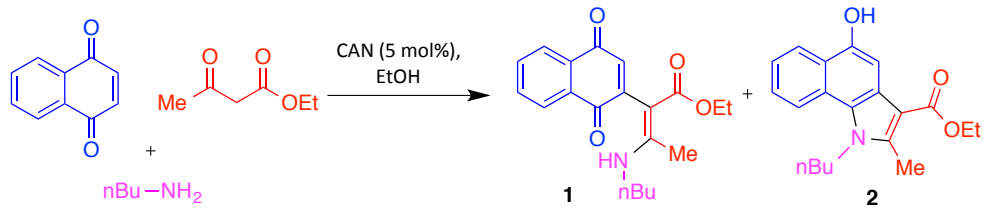
The sequential reaction between n-butylamine, ethyl acetoacetate and 1,4-naphthoquinone (Scheme 3.2), which was selected because it has received relatively little attention as a Nenitzescu substrate, was carried out in the

70 For a review of the use of CAN as a catalyst in organic synthesis, see: V. Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.,* **2010**, *110*, 3805.

71 For selected examples, see: (a) Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Org. Lett.,* **2008**, *10*, 4303. (b) V. Sridharan, S. Maiti and J. C. Menéndez, *Chem. Eur. J.,* **2009**, *15*, 4565-4572. (c) Sridharan, V.; Ribelles, P.; Ramos, M. T.; Menéndez, J. C. *J. Org. Chem.,* **2009,** *74*, 5715. (d) Sridharan, V.; Maiti, S.; Menéndez, J. C. *J. Org. Chem.* **2009**, *74*, 9365. (e) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Commun.* **2013**, *49*, 591. (f) Rocchi, D.; González, J. F.; Menéndez, J. C. *Green Chem.*, **2013**, *15*, 511.

72 Sridharan, V.; Avendano, C.; Menéndez, J. C. *Synlett,* **2007**, 881.

presence of a catalytic amount of CAN (5 mol%) at room temperature for 2 h. This reaction afforded quinone **1** (63%) as the major product, together with the fused indole **1** in 27% yield (Table 3.1, entry 1). When the reaction time was increased to 24 h, a complex mixture was obtained that contained only small amounts of **1** and **2** (entry 2). However, we were pleased to observe that, under reflux conditions, the reaction furnished compound **1** in 93% yield as the single product after one hour (entry 3). Increasing the reaction time to 1.5 h led only to a slight improvement in yield (entry 4), and the replacement of CAN by $InCl_3$ (10 mol %) as an alternative Lewis acid furnished the same product after a 2 h reflux without any significant change in the yield. We considered these improvements to have little significance and for this reason we retained for our subsequent reactions the 1 h reflux time and CAN as a catalyst because of its many previously mentioned advantages. No further catalyst exploration was deemed necessary.




**Scheme 3.2.** Model reaction used for the optimization studies

**Table 3.1.** Optimization of catalyst and reaction conditions

| Entry | Conditions | Yield of 1 (%) | Yield of 2 (%) |
|---|---|---|---|
| 1 | Rt, 2 h | 63 | 27 |
| 2 | Rt, 24 h | 0 | 0 |
| 3 | Reflux, 1 h | 0 | 93 |
| 4 | Reflux, 1.5 h | 0 | 96 |
| 5 | $InCl_3$ (10%), reflux, 2 h | 0 | 95 |

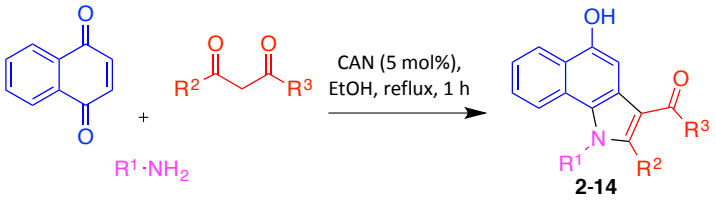
We next focused our attention on studying the effect of solvents, and to this end we carried out the model reaction under the previously established conditions and using a variety of solvents. As shown in Table 3.2, ethanol, acetonitrile, 1,2-dichloroethane and 1,4-dioxane were excellent solvents for the transformation. On the other hand, methanol, THF, dichloromethane, toluene and, specially, chloroform were less efficient, although these results are difficult to rationalize in terms of solvent polarity or solvation ability. In view of these results, we selected ethanol for further studies because of its low cost and toxicity and ready availability.

**Table 3.2.** Solvent optimization

| Entry | Solvent | Yield of 2 (%) |
|---|---|---|
| 1 | Ethanol | 93 |
| 2 | $CH_3CN$ | 92 |
| 3 | Methanol | 57 |
| 4 | THF | 66 |
| 5 | $CH_2Cl_2$ | 57 |
| 6 | 1-2-Dichloroethane | 93 |
| 7 | Toluene | 67 |
| 8 | 1,4-Dioxane | 90 |
| 9 | $CHCl_3$ | 28 |

### 3.2.2. Synthesis of benzo[*g*]indole derivatives

The optimized reaction conditions (5 mol% CAN, 1 h reflux, ethanol) were then applied to variety of 1,3-dicarbonyl compounds and amines that allowed structural variation at the $R^1$, $R^2$ and $R^3$ positions (Scheme 3.3).




**Scheme 3.3**. Synthesis of 5-hydroxybenzo[*g*]indole derivatives

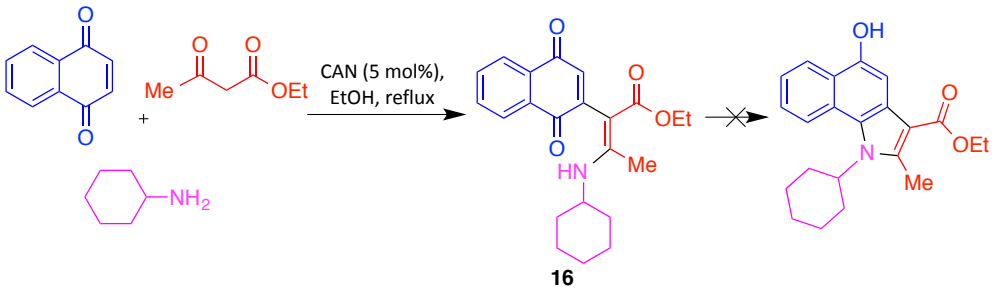
As shown in Table 3.3, the scope of the reaction included the use of β-ketoesters and β-keto thioesters as the dicarbonyl component and aliphatic primary amines (n-butyl, allyl, propargyl and benzyl amines, entries 1-8) or anilines having either electron-withdrawing or electron-releasing groups at the amine. All these substrates gave the target compounds in good to excellent yields with the sole exception of arylamines (entries 9-13), for

**Table 3.3.** Scope and yields of the Nenitzescu-type reaction

| Entry | Cmpd. | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|---|
| 1 | **2** | *n*-Bu | Me | OEt | 93 |
| 2 | **3** | *n*-Bu | Me | OMe | 96 |
| 3 | **4** | $CH_2$-CH=$CH_2$ | Me | OEt | 90 |
| 4 | **5** | $CH_2$-Ph | Me | OEt | 90 |
| 5 | **6** | $CH_2$-CH=$CH_2$ | Me | OMe | 89 |
| 6 | **7** | $CH_2$-CH=$CH_2$ | Me | S-$^t$Bu | 87 |
| 7 | **8** | $CH_2$-C≡CH | Me | S-$^t$Bu | 88 |
| 8 | **9** | $CH_2$-C≡CH | Me | OEt | 75 |
| 9 | **10** | Ph | Me | OEt | 65 |
| 10 | **11** | *p*-$MeOC_6H_4$ | Me | OEt | 55 |
| 11 | **11** | *p*-$MeOC_6H_4$ | Me | OEt | 73[a] |
| 12 | **12** | *p*-$ClC_6H_4$ | Me | OEt | 50 |
| 13 | **12** | *p*-$ClC_6H_4$ | Me | OEt | 76[a] |
| 14 | **13** | *n*-Bu | Me | S-$^t$Bu | 70 |
| 15 | **14** | *n*-Bu | *n*-Pr | OEt | 52 |

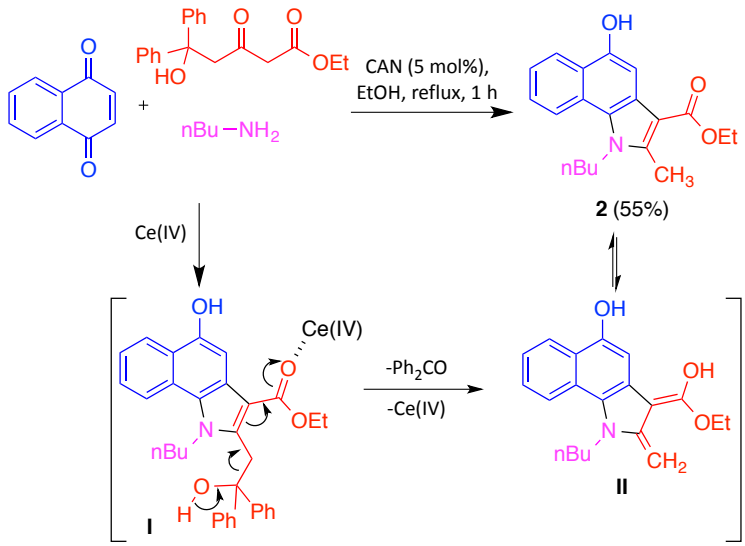
[a] The isolated enamines (**15**) were used as starting materials in these cases.

which yields were lower in the one-pot reaction due the low reactivity of these amines with 1,3-dicarbonyls in the enaminone formation step.[72] However, the problem could be solved by use of isolated, crude enamines (compounds **15**) as starting materials. An attempt to use cyclohexylamine, an α-branched primary amine, afforded only the corresponding intermediate **16** (72% yield after 1 h reaction time in the presence of CAN, 5 mol%), and all attempts to force its cyclization were unsuccessful (Scheme 3.4). Regarding the scope of the method in terms of the $R^2$ substituent, we verified that the reaction gave good results with alkyl groups (entry 15), but failed when $R^2$ was aryl.




**Scheme 3.4**. Attempted reaction involving cyclohexylamine

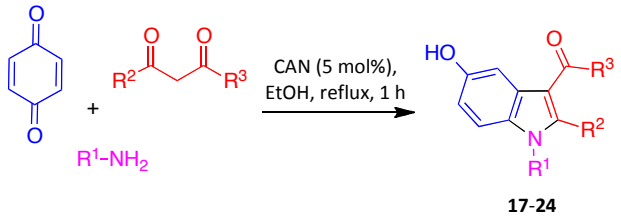
The reaction between n-butylamine, ethyl 5-hydroxy-3-oxo-5,5-diphenylpentanoate and 1, 4-naphthoquinone did not furnish the expected product, but gave instead the $C_2$-methyl derivative **2** in 55 % yield (Scheme 3.5). This reaction probably took place through the initial generation of the expected product **I**, which would be activated by coordination of the ester carbonyl with CAN to facilitate the elimination a molecule of benzophenone, giving the observed product *via* intermediate **II**.




**Scheme 3.5**. Side chain fragmentation in a reaction starting from a substrate containing a δ-hydroxy substituent

## 3.3. EXTENSION OF THE THREE-COMPONENT NENITZESCU REACTION TO THE SYNTHESIS OF 5-HYDROXYINDOLE DERIVATIVES

In order to further explore the scope of our three-component methodology, and also to facilitate its comparison with the standard Nenitzescu reaction, we studied its applicability to the reaction using *p*-benzoquinone, the most common Nenitzescu substrate that led to the expected 5-hydroxyindoles (compounds **17**-**24**) in very good yields (Scheme 3.6).




**Scheme 3.6**. Synthesis of 5-hydroxyindole derivatives via the three-component Nenitzescu reaction

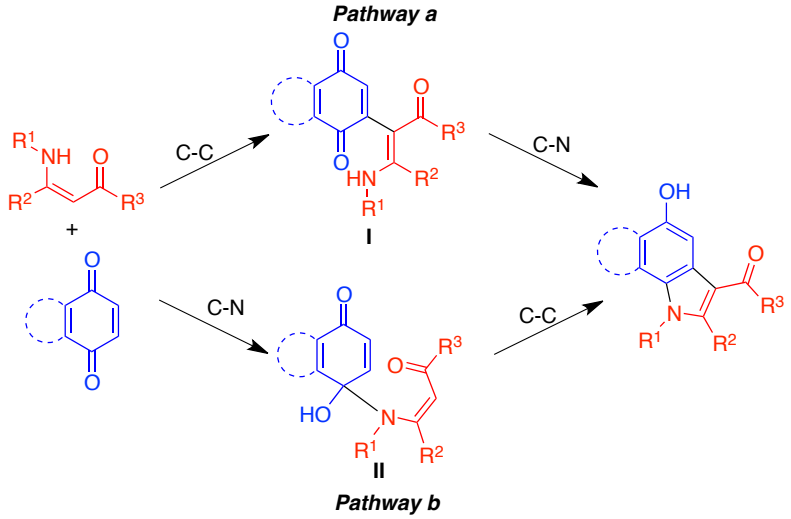
We verified that this reaction had a similar scope to the one starting from naphthoquinone, allowing the same types of substituents at $R^1$, $R^2$ and $R^3$ (Table 3.4). It is noteworthy that the reaction between amines, ethyl 3-oxohexanoate and *p*-benzoquinone gave particularly good yields of the corresponding indoles having a propyl substituent at position 2, showing an enhanced reactivity for *p*-benzoquinone compared with 1,4-naphthoquinone (entries 7 and 8).

**Table 3.4.** Scope and yields of the synthesis of 5-hydroxyindoles

| Entry | Compd | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|---|
| 1 | **17** | *n*-Bu | Me | OEt | 78 |
| 2 | **18** | $CH_2$-CH=$CH_2$ | Me | OEt | 75 |
| 3 | **19** | $CH_2$-Ph | Me | OEt | 73 |
| 4 | **20** | $CH_2$-C≡CH | Me | OEt | 69 |
| 5 | **21** | *n*-Bu | Me | S-$^t$Bu | 86 |
| 6 | **22** | $CH_2$-CH=$CH_2$ | Me | S-$^t$Bu | 81 |
| 7 | **23** | *n*-Bu | *n*-Pr | OEt | 82 |
| 8 | **24** | $CH_2$-CH=$CH_2$ | *n*-Pr | OEt | 78 |

## 3.4. MECHANISTIC PROPOSAL

A literature search on the mechanism of the Nenitzescu reaction revealed that there are two possible pathways.[67] In the first one (mechanism ***a***), the reaction is initiated by the formation of a carbon-carbon bond by the Michael addition of the enaminone to the quinone, giving **I**, followed by a cyclocondensation reaction that generates a carbon-nitrogen bond. The second possibility (mechanism ***b***) involves the initial generation of a carbon-nitrogen bond by condensation between the enamine nitrogen and the quinone carbonyl (intermediate **II**), followed by cyclization *via* an intramolecular Michael reaction to form the carbon-carbon bond (Scheme 3.7). In our case, we can rule out mechanism ***b*** in view of our isolation of intermediates **I** in many cases (*e.g.* compounds **1** and **16**).



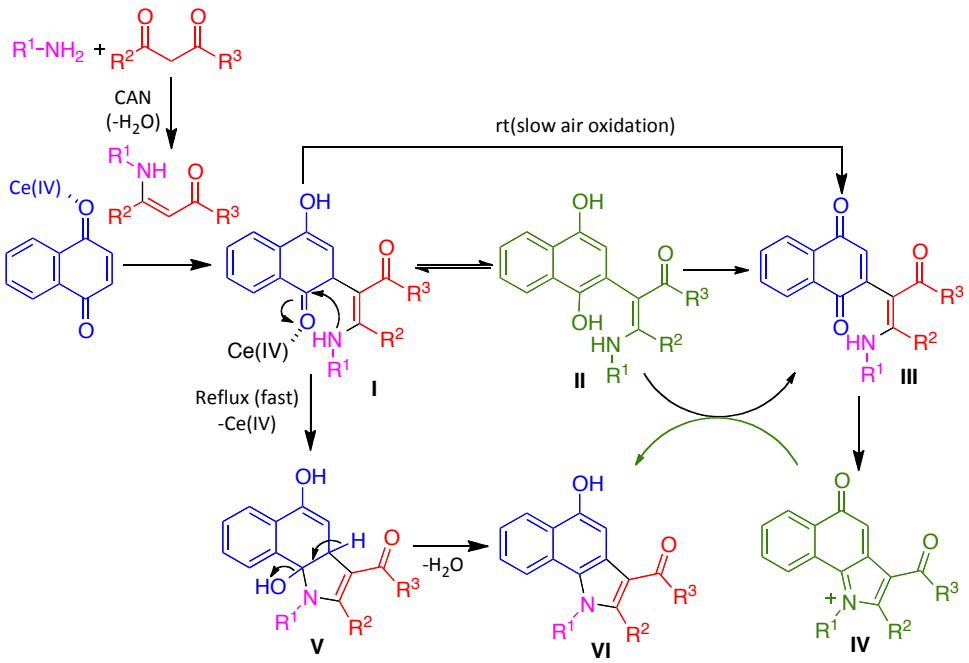

**Scheme 3.7**. The two possible mechanistic pathways in the Nenitzescu reaction

The mechanism normally accepted for route ***a*** conventionally involves a redox process which, applied to our case, would start by an initial Michael addition that affords intermediate **I**, followed by tautomerism to the

corresponding hydroquinone species **II**. Its oxidation by air to quinone **III**, even in small amounts, is enough to trigger a redox cycle in which **III** is cyclized to an iminium derivative **IV**, which is then reduced by hydroquinone **II** to give another molecule of **III** and the final product **VI**.[68c,73] However, this mechanism seems not to be in operation in our case since treatment of isolated compound **1**, a representative of structures **III**, with one equivalent of externally added hydroquinone under our standard reaction conditions (5 mol% of CAN in refluxing ethanol) did not afford the corresponding Nenitzescu product **2**. Based on these observations, we propose the alternative mechanism shown in Scheme 3.8, not involving any redox process. Thus, the enaminone formed in the reaction between the starting amine and 1,3-dicarbonyl compound adds to the CAN-activated naphthoquinone to afford intermediate **I**, which at room temperature is slowly converted by air oxidation into the *p*-quinone derivative **III**, which has been isolated in some cases. In a parallel process, under our optimized conditions involving reflux temperature, intermediate **I** undergoes a fast intramolecular nucleophilic cyclization before tautomerism, prompted by coordination of Ce(IV) to its carbonyl group,[74] and this is followed by elimination of a molecule of water to furnish the observed products, the fused indoles **VI**.

73 For mechanistic discussions of the Nenitzescu reaction involving redox processes, see: (a) Kuckländer, U. *Tetrahedron* **1972**, *28*, 5251. (b) Patrick, J. B.; Saunders, E. K. *Tetrahedron Lett*., **1979**, *20*, 4009. (c) Bernier, J.-L.; Hénichart, J.-P. *J. Org. Chem*., **1981**, *46*, 4197.

74 For an example of a Lewis acid-catalyzed Nenitzescu reaction, see: Velezheva, V. S.; Kornienko, A. G.; Topilin, S. V.; Turashev, A. D.; Peregudov, A. S.; Brennan, P. *J. Heterocycl. Chem*., **2006**, *43*, 873.




**Scheme 3.8**. Mechanism proposed for the CAN-catalyzed multicomponent Nenitzescu reaction. Intermediates **II** and **IV** in green are believed not to be formed

## 3.5. POST-CONDENSATION MANIPULATION OF THE NENITZESCU PRODUCTS. SYNTHESIS OF TETRACYCLES DERIVED FROM THE 9,12-DIHYDRO-8*H*-AZEPINO[1,2-$a$]BENZO[*g*]INDOLE RING SYSTEM

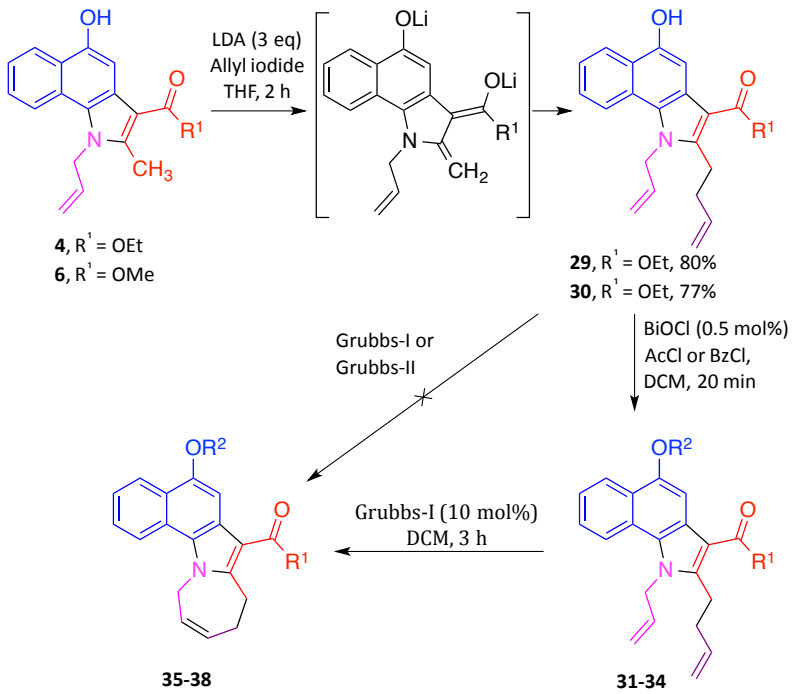
At this stage, we reasoned that the functionality present in compounds **2**-**14** should allow their use as starting materials for novel routes to structurally complex nitrogen heterocycles. Indeed, the combination of multicomponent processes with postcondensation complexity-generating reactions is known as the build-couple-pair approach to diversity-oriented synthesis.[75] For instance, a ring-closing metathesis reaction between suitable substituents placed at the indole nitrogen and the adjacent methyl group should provide ready access to unusual tetracyclic compounds bearing a bridgehead nitrogen atom.

In order to translate this idea into practice, we examined the possibility of using the acidity of the carbonyl-conjugated 2-methyl group of our fused indoles to introduce terminal alkenyl and alkynyl chains *via* a deprotonation-nucleophilic substitution sequence, although this type of deprotonation of 2-methylindoles has received little attention in the literature.[76] In the event, we discovered that treatment of N-allyl derivatives of compounds **4** and **6** with LDA in THF followed by addition of allyl iodide smoothly afforded the desired metathesis precursors **25** and **26** in high yields (Scheme 3.9). These alkylation reactions can be presumed to occur on dianion species generated by deprotonation of both the phenol and the $C_2$-methyl group and, interestingly, were completely regioselective in favour of the latter.

75 (a) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56. (b) Schreiber, S. L. *Nature* **2009**, *457*, 153–154.

76 For selected examples, see: (a) Rao, M. V.; Basaveswara, S.; Satyanarayana, J.; Ila, H.; H. Junjappa, H. *Tetrahedron Lett.,* **1995**, *36*, 3385. (b) Joseph, B.; Cornec, O.; Merour, J.-Y. *Tetrahedron,* **1998**, *54*, 7765. (c) Mouaddib, A.; Joseph, B.; Aissa, A.; Merour J.-Y.; Leonce, S. *Heterocycles*, **1999**, *51*, 2127.

All efforts to achieve the ring-closing metathesis (RCM) and ring-closing enyne metathesis (RCEYM) reaction of **25** and **26** using Grubbs catalysts were unsuccessful. Fortunately, as shown in Scheme 3.9 and Table 3.5, the *O*-acylated derivatives **27**-**30**, prepared under remarkably mild conditions in the presence of bismuth oxychloride, underwent a smooth ring-closing reaction in the presence of 10 mol % of Grubbs first generation catalyst at room temperature in dichloromethane to give very good yields of compounds **31**-**34**, which are derivatives of the hitherto unknown 9,12-dihydro-8*H*-azepino[1,2-*a*]benzo[*g*]indole ring system and are of potential biological interest in view of the varied biological activities known for pyrrolo[1,2-*a*]azepine derivatives.[77] This efficient transformation is




**Scheme 3.9.** Synthesis of 9,12-dihydro-8*H*-azepino[1,2-*a*]benzo[*g*]indoles *via* ring-closing metathesis

77 Bonanni, M.; Marradi, M.; Cardona, F.; Cicchi, S.; Goti, A. *Beilstein J. Org. Chem.*, **2007**, *3*, 44 and references therein.

**Table 3.5.** Results of the allylation and metathesis reactions

| Entry | $R^1$ | $R^2$ | Allylation step | | RCM step | |
|---|---|---|---|---|---|---|
| | | | Cmpd | Yield (%) | Cmpd | Yield (%) |
| 1 | OEt | Ac | **27** | 95 | **31** | 80 |
| 2 | OMe | Ac | **28** | 94 | **32** | 77 |
| 3 | OEt | Bz | **29** | 80 | **33** | 77 |
| 4 | OMe | Bz | **30** | 82 | **34** | 76 |

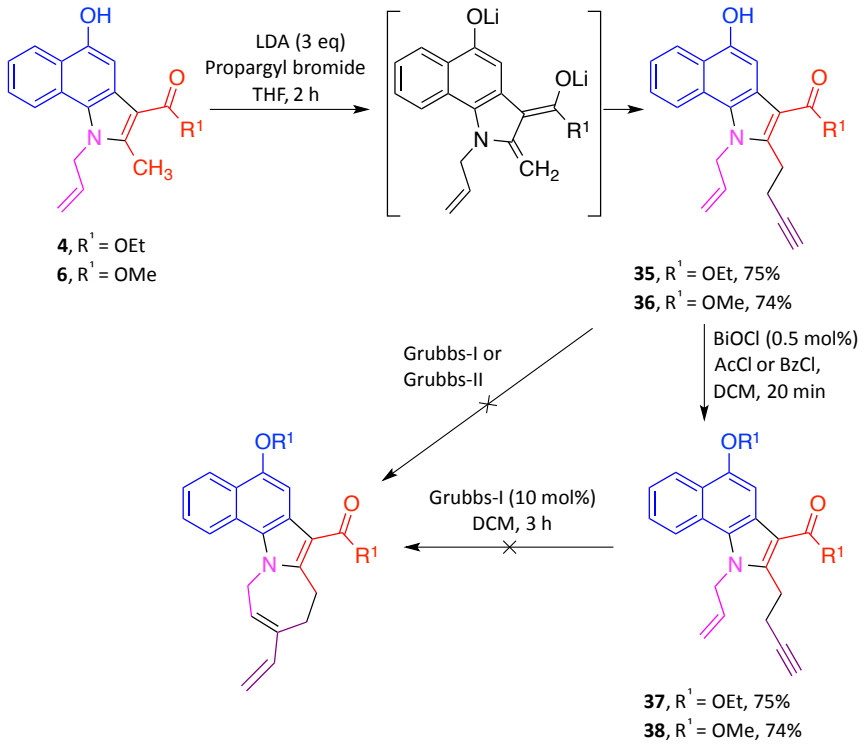
noteworthy in view of the difficulties often associated with the construction of medium-sized rings by RCM, specially from acyclic precursors, owing to entropic factors and transannular repulsions that develop as the ring is formed.[78] Indeed, to our knowledge, the synthesis of compounds **31**-**34** constitutes the first example of the preparation of a pyrrolo[1,2-*a*]azepine system by a metathesis strategy.

We also planned ring-closing enyne metathesis (RCEYM) reactions (Scheme 3.10), which, from the point of view of the generation of molecular diversity, have the advantage of providing a conjugate diene moiety that can be used for further complexity-generating reactions. To this end, we prepared the starting materials **37** and **38** using the methods described above. Unfortunately, the attempted RCEYM reactions of these compounds gave only traces of the desired products, even after assaying a variety of commercially available metathesis catalysts in different solvents including the highly effective fluorinated aromatic hydrocarbon solvents,[79]

78 For a review of the synthesis of oxygen and nitrogen heterocycles using ring-closing metathesis reactions, see: Deiters, A.; Martin, S. F. *Chem. Rev*., **2004**, *104*, 2199.

79 Samojowicz, C.; Bieniek, M.; Zarecki, A.; Kadyrov, R.; Grela, K. *Chem. Commun,* **2008**, 6282.

and also failed under an ethylene atmosphere, which is often used to promote enyne metathesis reactions.[80]



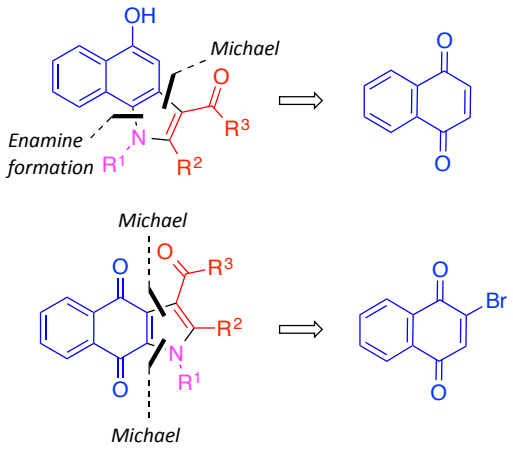

**Scheme 3.10.** Attempted ring-closing enyne metathesis (RCEYM) reactions

80 For the acceleration of RCEYM reactions in an ethylene atmoshphere, see: (a) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.,* **1998**, *63*, 6082. (b) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.,* **2002**, *4*, 803. (c) Nuñez, A.; Cuadro, A. M.; Álvarez-Builla, J.; Vaquero, J. J. *Chem. Commun.,* **2006**, 2690.

# 4. Variations of the multicomponent Nenitzescu reaction

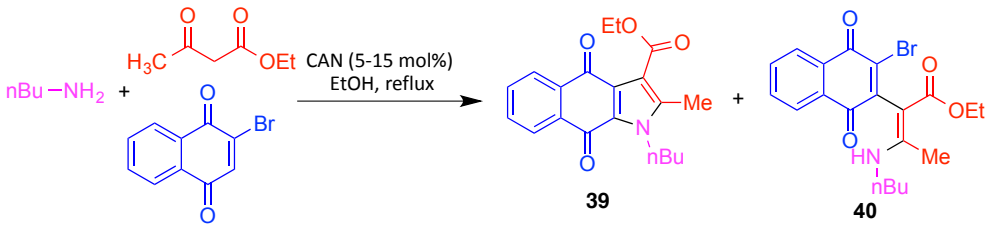
## 4.1. SYNTHESIS OF LINEARLY FUSED INDOLES BY MICHAEL-MICHAEL DOMINO MULTICOMPONENT REACTIONS: PREPARATION OF BENZO[*f*]INDOLEQUINONE DERIVATIVES

When considering mechanism of the Nenitzescu reaction under our conditions (Scheme 3.8), we wondered if we would be able to deviate the Michael-enamine formation process so far studied to a Michael-Michael domino sequence, leading to a method for the preparation of linear tricyclic systems. We considered that this goal might be feasible if we increased the reactivity of the quinone double bond by introducing a leaving group at its C-2 position (Scheme 4.1). In other words, we set out to study the outcome of our three-component reactions when using 2-bromonaphthoquinone as substrate.




**Scheme 4.1**. Our plan to deviate the three-component process to afford linearly fused indoles instead of the Nenitzescu products

Encouragingly, our starting hypothesis proved correct and when we applied our usual three-component protocol to butylamine, ethyl acetoacetate, and 2-bromonaphthoquinone[81] as the Michael acceptor, we observed the formation of indolequinone **39** as the main product together with aminoquinone **40**, which can be regarded as an intermediate of the pathway leading to **39** (Scheme 4.2 and Table 4.1, entry 1). Changes in the reflux time and catalyst load led to very similar results (entries 2-4), although prolonged reaction times led to decomposition (entry 5). Interestingly, we found that the reaction could be performed at room temperature, although with a worse **39**/**40** ratio (entry 6).




**Scheme 4.2**. Three-component synthesis of benzo[*f*]indolequinone derivative **39**

81 For the synthesis of 2-bromonaphthoquinone, see: P. Bachu, J. Sperry and M. A. Brimble, *Tetrahedron*, **2008**, 64, 4727-4834.

**Table 4.1.** Optimization of the synthesis of compound **40**

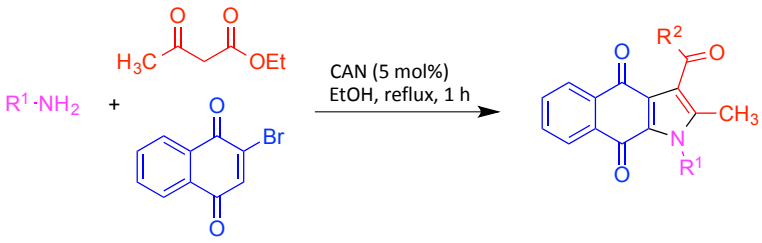
| Entry | CAN (%) | Time (h) | % 1 | % Fused indole |
|---|---|---|---|---|
| 1 | 5 | 1 | 21 | 50 |
| 2 | 5 | 3 | 17 | 39 |
| 3 | 5 | 1 | 18 | 54[a] |
| 4 | 15 | 2.5 | 12 | 50 |
| 5 | 5 | 24 | 0 | 0[b] |
| 6 | 5 | 1 | 17 | 51[c] |

[a]Isolated, crude enamine was used. [b]Decomposed. [c]Isolated enamine was used and the reaction was carried out at room temperature.

Under the optimal conditions, the use of a β-diketone as the dicarbonyl component was next assayed. Thus, the reaction between butylamine, 2-bromonaphthoquinone and acetylacetone afforded the fused indolequinone **41** as the only product in 67% yield (Table 4.2, entry 2). Some other 3-acetyl derivatives of the target tricyclic system (compounds **42**-**44**) were accesible by changing the primary amine (entries 3-5). It is noteworthy that literature precedent for a Nenitzescu reaction between 2-chloroanthracene-1,4,9,10-tetraone and a β-enaminone in acetic acid proceeded through the standard pathway, affording an angularly fused indole related to the anthracyclines.[82] On the other hand, a few examples of two-component reactions between β-enaminones and bromoquinones that give linear products related to ours are known in the literature, but they required Ullman-type conditions ($K_2CO_3$, $CuBr_2$) and proceed only in 15-25% yields.[83]

82 Schenck, L. W.; Kuna, K.; Frank, W.; Albert, A.; Asche, C.; Kucklaender, U. *Bioorg. Med. Chem.,* **2006**, 14, 3599.

83 O'Sullivan, P. J. *Tetrahedron Lett.,* **1992**, 33, 535.




**Scheme 4.3**. Three-component synthesis of benzo[*f*]indolequinones **39** and **41**-**44**

**Table 4.2.** Scope and yields of the synthesis of benzo[*f*]indolequinone derivatives

| Entry | Compd | $R^1$ | $R^2$ | % Fused indole |
|---|---|---|---|---|
| 1 | **39** | *n*-Bu | OEt | 54[a] |
| 2 | **41** | *n*-Bu | Me | 67 |
| 3 | **42** | $CH_2$-Ph | Me | 51 |
| 4 | **43** | $CH_2$-CH=$CH_2$ | Me | 44 |
| 5 | **44** | $CH_2$-C≡CH | Me | 42 |

[a] Together with 18% of compound **40**.

## 4.2. SYNTHESIS OF *ORTHO*-QUINONES DERIVED FROM THE BENZO[*g*]INDOLE RING SYSTEM

Quinones are a very important class of compounds owing to the relevance of the biochemical roles of compounds such as ubiquinone, plastoquinone and phylloquinone (vitamin $K_1$). Furthermore, quinone moieties are essential structural fragments of a large number of pharmacologically active compounds, specially in the anticancer field.[84] Due to the fact that heterocycles are the most important single class of compounds in the pharmaceutical and agrochemical industries, comprising around 60% of all drug substances in therapeutic use, heterocyclic quinones can be considered as particularly relevant.[85] Indole-4,7-quinones related to the natural product mitomycin are well known as anticancer agents acting by alkylation of the DNA minor groove.[86] The mitosenes, such as WV15 and the aziridinylindolequinones, such as EO9, constitute typical examples. On the other hand, *ortho*-quinones derived from indole frameworks are not very common. Probably the most important one is pyrroloquinoline-quinone (PQQ), which plays crucial roles as a cofactor and is involved in a range of biochemical reactions including oxidative deaminations and free-radical redox reactions (Figure 4.1).[87]

84 For reviews of DNA alkylating agents containing quinone structural fragments, see: (a) Begleit, A. *Front. Biosci*. **2000**, *5*, 153. (b) Hargreaves, R. H. J.; Hartley, J. A.; Butler, J. *Front. Biosci*. **2000**, *5*, 172. (c) Beall, H. D.; Winski, S. L. *Front. Biosci.* **2000**, *5*, 639.

85 For selected reviews of heterocyclic quinones, see: (a) Middleton, R. W.; Parrick, J. in Patai, S.; Rappoport, Z. (Eds.), The chemistry of quinonoid compounds, vol. 2, p. 1099. John Wiley & Sons, 1988. (b) Tisler, M. *Adv. Heterocycl. Chem.* **1989**, *45*, 37. (c) Sissi, C.; Palumbo, M. *Curr. Top. Med. Chem*. **2004**, *4*, 219. (d) Garuti, L.; Roberti, M.; Pizzirani, D. *Mini-Rev. Med. Chem*. **2007**, *7*, 481. (e) Colucci, M. A.; Couch, G. D.; Moody, C. J. *Org. Biomol. Chem*. **2008**, *6*, 637.

86 Avendaño, C.; Menéndez, J. C. Medicinal Chemistry of Anticancer Drugs, chapter 6. Elsevier, Oxford, 2008.

87 For a review, see: Stites, T. E.; Mitchell, A. E.; Rucker, R. B. *J. Nutrition* **2000**, *130*, 719.

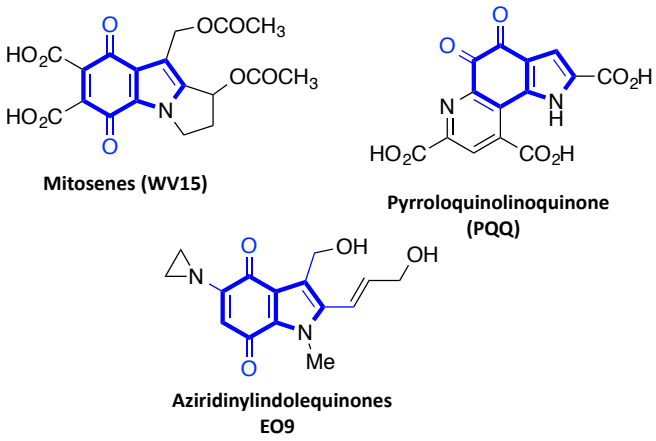
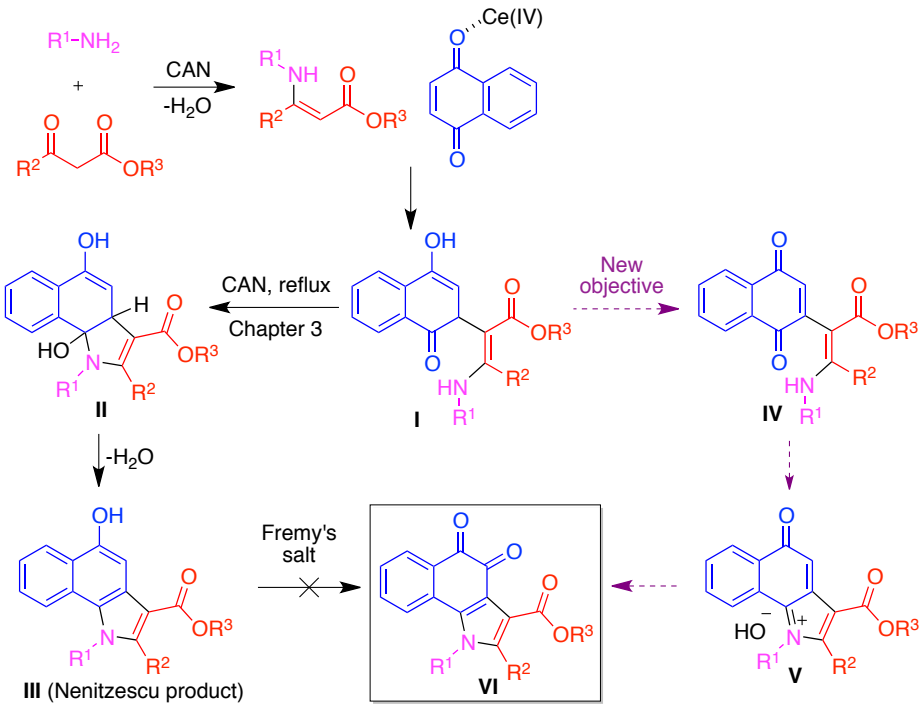



**Figure 4.1.** Some biologically relevant indolequinones

In this context, we became interested in developing a route for the synthesis of indole derivatives containing an *ortho*-quinone moiety, based on our Nenitzescu-type chemistry. As shown during our initial optimization studies described in chapter 3, the CAN-catalyzed, three-component reaction between primary amines, β-dicarbonyl compounds and naphthoquinone can follow two competitive pathways, leading to the Nenitzescu product **III** *via* intermediates **I** and **II** or to Michael adducts **IV**, the latter usually in small amounts. we became intrigued by the possibility of using this chemistry for the preparation of *ortho*-quinone derivatives. More specifically, we wished to ascertain whether compounds **IV** might be suitable precursors to iminium derivatives **V**, the putative intermediates of the conventional redox mechanism. We reasoned that, in the absence of reductive species, these intermediates should behave as excellent Michael acceptors able to trap hydroxide, acting as a nucleophile, thereby afording compounds dioxygenated at the 4 and 5 positions of the indole ring, which should be easy to transform into the target *ortho*-quinones **VI** (Scheme 4.4). It is relevant to mention at this point that this transformation was rendered particularly significant by the observation that we were unable to

obtain compounds **VI** from **III** by oxidation with Fremy's salt under a variety of conditions.[88] We were also encouraged to attempt this transformation by the fact that the benzo[*g*]indole-4,5-dione framework present in **VI** is almost unknown in the literature, and its preparation normally requires multistep sequences.[89,90] There is a report of the synthesis of three benzo[*g*]indole-4,5-diones in a two-step sequence from 2,3-dichloronaphthoquinone and N-substituted β-aminocrotonic esters, but it has very clear disadvantages, including the need to prepare the starting




**Scheme 4.4**. Our plan for the synthesis of *ortho*-indolequinones **VI**

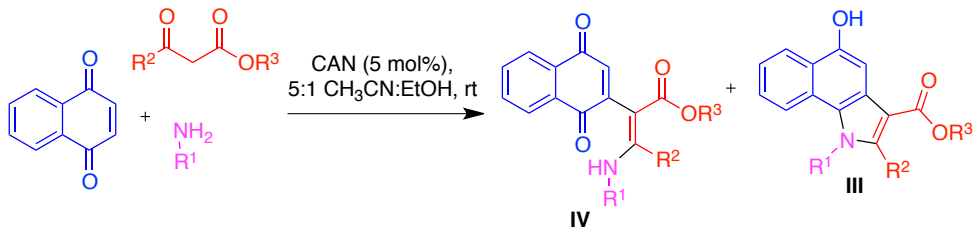
88 López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *J. Chem. Soc. Perkin Trans. 1* **1997**, 229.

89 (a) Nesterova, I. N.; Grinev, A. N.; Rubtsov, N. M. *Khim. Geterosikl. Soed.* **1989**, 66 and references therein. (b) Itoh, S.; Fukui, Y.; Ogino, M.; Haranou, S.; Komatsu, M.; Ohshiro, Y. *J. Org. Chem.* **1992**, *57*, 2788. (c) Suginome, H.; Sakurai, H.; Sasaki, A.; Takeuchi, H.; Kobayashi, K. *Tetrahedron* **1994**, *50*, 8293.

90 A synthesis of a cyclohexane-fused derivative of **V** has been recently described, although it was a side product isolated in low yield. See: Otero, J. M.; Barcia, J. C.; Salas, C. O.; Thomas, P.; Estévez, J. C.; Estévez, R. J. *Tetrahedron* **2012**, *68*, 1612.

enaminones in a separate step, its very narrow scope, its poor atom economy owing to the release of two molecules of HCl and the very harsh reaction conditions required for the cyclization step, which led to "strong resinification of the reaction medium".[91]

As a first step towards our goal, we needed to establish reliable conditions for the preparation of compounds **IV**, bearing in mind the competition with the formation of the Nenitzescu products **III**. After extensive manipulation of the reaction conditions, we established that the best option to shift the processes summarized in Scheme 4.5 towards the formation of **IV** involved the reaction between primary amines, β-ketoesters and naphthoquinone in the presence of 5% CAN, at room temperature in a flask open to the air to facilitate the oxidation of intermediate hydroquinone species and using as solvent a 5:1 mixture of acetonitrile and ethanol. Under these conditions, the **IV**/**III** ratios between the desired naphthoquinones and the Nenitzescu products ranged betwen 85:15 and 65:35 (Table 4.3). The intermediacy of an enaminone species was verified by carrying out the reaction from an isolated example of such an enaminone, prepared by a method previously developed by our group that also involves the use of CAN as catalyst.[92]




**Scheme 4.5.** Synthesis of benzoquinone derivatives **IV**

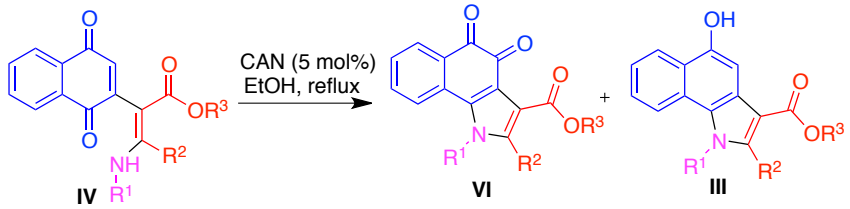
91 Nesterova, I. N.; Grinev, A. N.; Rubtsov, N. M. *Khim. Geterotsikl. Soedin.* **1989**, 66.
92 Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Synlett* **2007**, 881.

**Table 4.3.** Results obtained in the synthesis of quinones **IV**

| Entry | Compd | $R^1$ | $R^2$ | $R^3$ | Time, h | IV/III ratio[a] | Yield of IV (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **40** | *n*-Bu | Me | Et | 1.5 | 85:15 | 65 |
| 2 | **45** | *n*-Bu | Me | $^t$Bu | 1 | 80:20 | 68 |
| 3 | **46** | $CH_2$-CH=$CH_2$ | Me | Et | 1 | 75:25 | 62 |
| 4 | **47** | *n*-Bu | Me | Me | 1.51 | 75:25 | 60 |
| 5 | **48** | *n*-Bu | Me | $CH_2$-CH=$CH_2$ | 1.5 | 78:22 | 65 |
| 6 | **49** | *n*-Pr | Me | Et | 1 | 70:30 | 58 |
| 7 | **50** | $CH_2$-Ph | Me | Et | 1.5 | 65:35 | 62 |
| 8 | **51** | *n*-Bu | n-Pr | Et | 1 | 65:35 | 60 |

[a]Determined on the crude $^1$H NMR spectra. [b]Isolated yields after chromatography.

With adequate amounts of compounds **IV** in hand, we could study the final step of our route. After some experimentation, we discovered that a simple reflux in ethanol containing CAN allowed their one-pot transformation into the target *ortho*-quinones **VI**, again with small amounts of the Nenitzescu compounds **III** as side products (Scheme 4.6 and Table 4.4).




**Scheme 4.6.** Synthesis of *ortho*-indolequinone derivatives **VI**

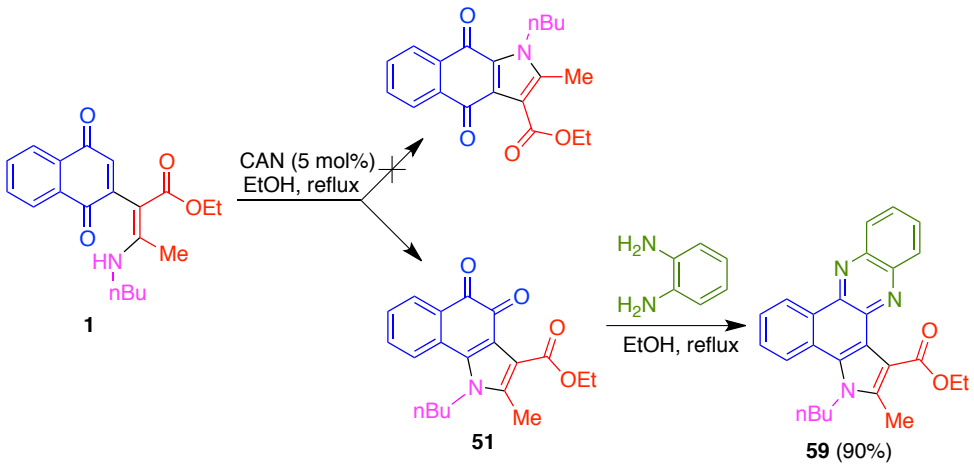
**Table 4.4**. Scope and yields in the synthesis of *ortho*-indolequinones **VI** (**51**-**58)**

| Entry | Compd | $R^1$ | $R^2$ | $R^3$ | Time, h | VI/III ratio[a] | Yield of VI (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **52** | *n*-Bu | Me | Et | 2 | 75:25 | 61 |
| 2 | **53** | *n*-Bu | Me | $^t$Bu | 1 | 70:25 | 55 |
| 3 | **54** | $CH_2$-CH=$CH_2$ | Me | Et | 2 | 85:15 | 56 |
| 4 | **55** | *n*-Bu | Me | Me | 0.5 | 65:35 | 58 |
| 5 | **56** | *n*-Bu | Me | $CH_2$=$CHCH_2$ | 1 | 73:27 | 55 |
| 6 | **57** | *n*-Pr | Me | Et | 2 | 75:25 | 59 |
| 7 | **58** | $CH_2$-Ph | Me | Et | 2 | 80:20 | 57 |
| 8 | **59** | *n*-Bu | *n*-Pr | Et | 1 | 85:15 | 60 |

[a]Determined on the crude $^1$H NMR spectra, [b]Isolated yields after chromatography

The spectral data, specially the very close chemical shifts for the carbonyl $^{13}$C-NMR signals,[88,93] fitted the expected *ortho*-quinone structure for the final products, but in view of the possibility of a cyclization pathway leading to a regioisomeric linear para-quinone system *via* an aza-Michael addition of the enamine nitrogen onto the quinone moiety in compounds **IV**, we considered it desirable to have independent chemical evidence for the presence of an *ortho*-quinone unit in our reaction products. To achieve this goal, we treated **52** with *o*-phenylenediamine in refluxing ethanol, and this reaction afforded the fused quinazoline derivative **60** in 90% yield, a result that confirmed the *ortho*-quinone structure (Scheme 4.7).

93 Rajesh, S. M.; Bala, B. D.; Perumal, S.; Menéndez, J. C. *Green Chem.* **2011**, *13*, 3248.




**Scheme 4.7.** Verification of the angular *ortho*-quinone structure of compound **52**

# 5. Multicomponent synthesis of arenoquinolizines from acyclic precursors

## 5.1. INTRODUCTION

The benzo[*a*]quinolizine and indolo[2,3-*a*]quinolizine ring systems are key structural feature in a large number of alkaloids exhibiting a wide range of biological activities.[94] Some representative examples are summarized in Figures 5.1 and 5.2.

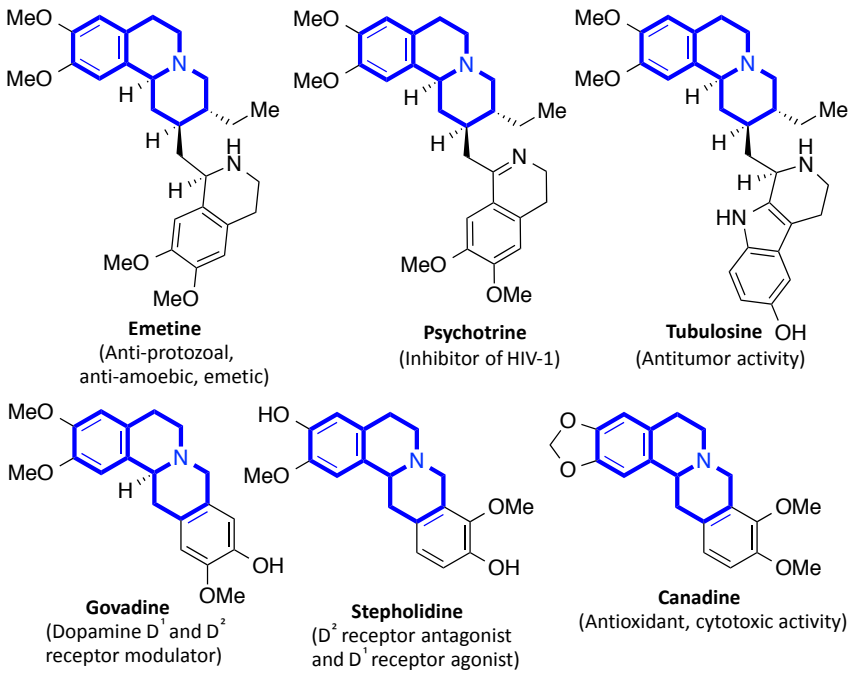



**Figure 5.1**. Examples of alkaloids containing a benzo[*a*]quinolizidine subunit

94 (a) Cordell, G. A. In *The Alkaloids: Chemistry and Biology;* Ed.; Academic Press: New York, **1998**, Vol. 50 (b) Avendaño, C.; Menéndez, J. C. in *Comprehensive Heterocyclic Chemistry III*, Vol. 12, Jones, K. volume ed.; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. general eds.; Elsevier, Oxford, **2008**, Chapter 1.

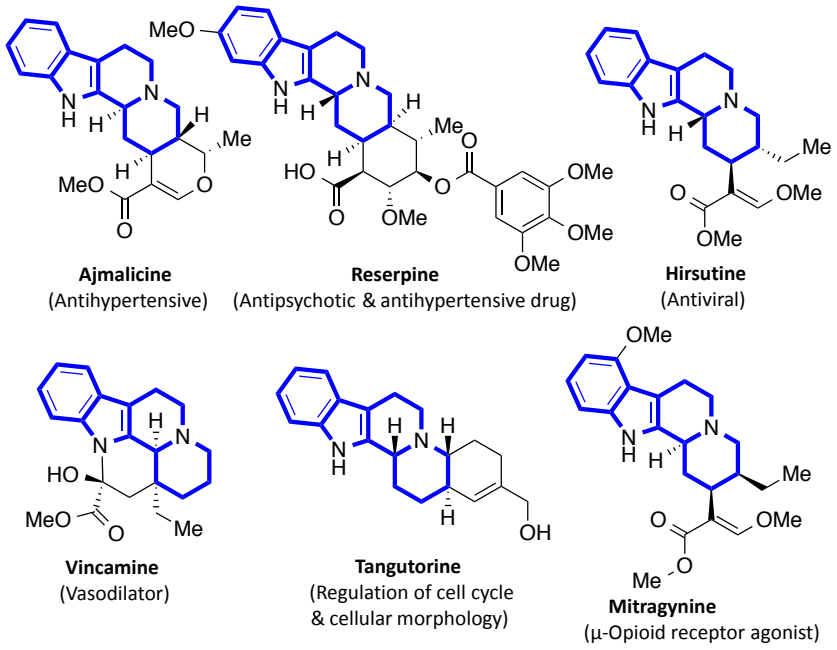
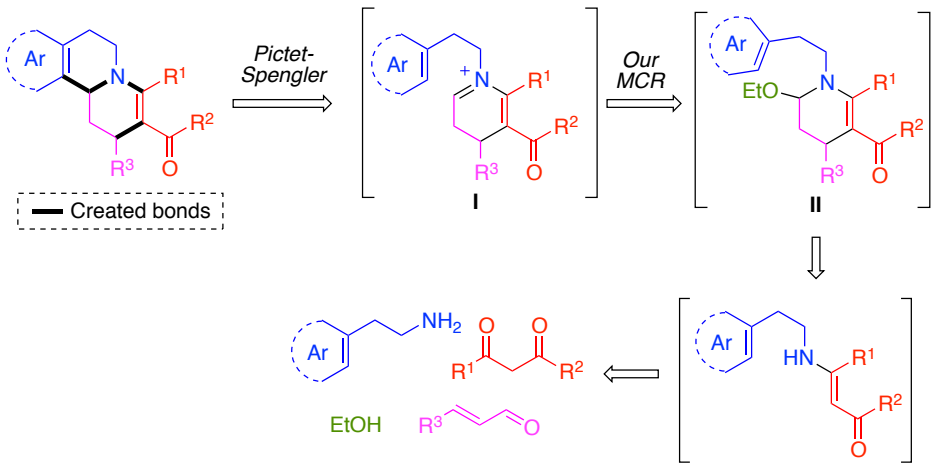



**Figure 5.2**. Examples of alkaloids containing an indolo[2,3-*a*]quinolizidine subunit

As mentioned in Chapter 1, our group has developed a CAN-catalyzed four-component reaction that allows the one-pot, efficient preparation of 1-alkyl-6-ethoxy-1,4,5,6-tetrahydropyridines from primary amines, β-dicarbonyl compounds, α,β-unsaturated aldehydes and primary alcohols *via* a formal aza[3+3]cycloaddition between a β-enaminone intermediate and the α,β-unsaturated aldehyde, followed by reaction of the resulting hemiaminal with ethanol.[95] One of the goals of the present thesis was to adapt this reaction to the synthesis of the areno[*a*]quinolizine frameworks, and to this end we sought to combine our tetrahydropyridine preparation with a Pictet–Spengler reaction, thus achieving a domino process leading to the direct, one-pot preparation of a variety of areno[*a*]quinolizines from open-chain precursors. The process involves the generation of two C-C and two C-N bonds through formation of the iminium cation **I** from the initial

95 Sridharan, V.; Maiti, S.; Menéndez, J. C. *Chem. Eur. J.* **2009**, *15*, 4565.

tetrahydropyridine derivative **II** (Scheme 5.1). At this stage, it was not clear whether we would be able to perform this domino sequence in a single operation or if we would need to isolate the intermediate tetrahydropyridine **II**.




**Scheme 5.1**. Our MCR plan for the one-pot synthesis of areno[*a*]quinolizines

It must be mentioned that a mechanistically unrelated, two-step method has been previously described in the literature for the synthesis of areno[*a*]quinolizines that involves the preparation of a cyclic hemiacetal from a β-dicarbonyl compound and an α,β-unsaturated aldehyde. The subsequent reaction of this hemiacetal with tryptamine in the presence of a Brønsted acid affords the target product, probably through a Pictet–Spengler reaction, and the use of chiral Brønsted acids has been investigated and found to lead to good enantioselections in some cases.[96] Although less directly related to our work, we will also mention the reaction between β-amidoesters derived from tryptamine and α,β-

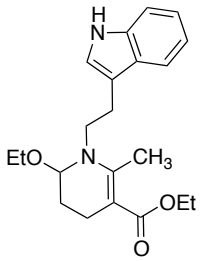
96 (a) Wu, X.; Dai, X.; Nie, L.; Fang, H.; Chen, J.; Ren, Z.; Cao, W.; Zhao, G. *Chem. Commun.*, **2010**, *46*, 2733.. (b) X. Wu, H. Fang, Q. Liu, L. Nie, J. Chen, W. Cao, G. Zhao, *Tetrahedron* **2011**, *67*, 7251.

unsaturated aldehydes, which affords lactams derived from the indolo[2,3-*a*]quinolizidin-4-one system.[97]

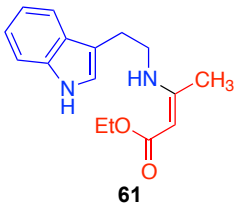
97 (a) Franzén, J.; Fisher, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 787. (b) Zhang, W.; Franzén, J. *Adv. Synth. Catal.* **2010**, *352*, 499. (c) Zhang, W.; Bah, J.; Wohlfarth, A.; Franzén, J. *Chem. Eur. J.* **2011**, *17*, 13814. (d) Dai, X.; Wu, X.; Fang, H.; Nie, L.; Chen, J.; Deng, H.; Cao, W.; Zhao, G. *Tetrahedron* **2011**, *67*, 3034.

## 5.2. SYNTHESIS OF INDOLO[2,3-*a*]QUINOLIZINES

Our initial experiments involved tryptamine, ethyl acetoacetate and acrolein ($R^3$ = H). In these reactions, a complex mixture was obtained where signals corresponding to tetrahydropyridine (**I**) were observed. This compound could not be brought to pure state because of its low stability and all our attempts at the Pictet-Spengler cyclization of the crude materials under acidic conditions led only to very complex mixtures. We then examined the reaction involving cinnamaldehyde, and found that our usual conditions (CAN, acetonitrile, room temperature) gave the β-enaminone (compound **61**) derived from tryptamine and ethyl acetoacetate, but the reaction did not progress to the tetrahydropyridine stage (Table 5.1, entry 1). The use of indium trichloride as the catalyst did not change this result (entry 2).



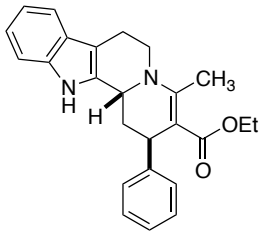

**I**




**61**

When the solvent was replaced by ethanol, a reaction was observed which, most interestingly, afforded the target final product **62** (entry 3). In spite of the low yield, this result was very encouraging in that it proved that it should be possible to effect the desired transformation in a single synthetic operation. Indeed, we found that simply by carrying out the reaction under reflux conditions we were able to isolate compound **62** in 86% yield (entry 4). The use of other alcohols (methanol, 2-propanol) as solvents was also

examined, but we found no improvement (entries 5 and 6). Results similar to those achieved with CAN were obtained using indium trichloride in ethanol (entries 7 and 8), but we decided to employ the cerium catalyst for additional studies in view of its lower cost and better stability.



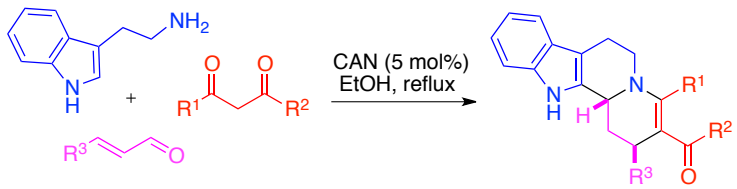

**62**

**Table 5.1.** Optimization of conditions for the synthesis of compound **62**

| Entry | Solvent | Conditions | Yield (%) |
|---|---|---|---|
| 1 | $CH_3CN$ | CAN (5%), rt, 1 h | 0[a] |
| 2 | $CH_3CN$ | $InCl_3$ (5%), rt, 1 h | 0[a] |
| 3 | EtOH | CAN (5%), rt, 1 h | 35[b] |
| 4 | EtOH | CAN (5%), reflux, 1.5 h | 86 |
| 5 | MeOH | CAN (5%), reflux, 1.5 h | 35 |
| 6 | $^{i}$PrOH | CAN (5%), reflux, 1.5 h | 75 |
| 7 | EtOH | $InCl_3$ (5%), rt, 1 h | 45 |
| 8 | EtOH | $InCl_3$ (5%), reflux, 1 h | 87 |

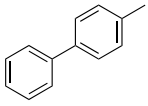
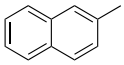
[a]The enaminone derived from tryptamine and ethyl acetoacetate was obtained,
[b]The isolated enaminone was used as the starting material

With the optimized conditions in hand, we explored the scope of the reaction (Scheme 5.2 and Table 5.2). Regarding the carbonyl function, we successfully assayed esters (entries 1-10, 12 and 13), thioester (entry 11) and ketones (entries 14-16). The reaction also allowed all kinds of aromatic $R^3$ substituents, including unsubstituted phenyl (entries 1, 2 and 11-16), phenyl groups bearing electron-withdrawing (entries 4 and 6) and electron-releasing (entry 5) substituents, 4-biphenyl (entry 3), 2-furyl (entry 7) and




**Scheme 5.2.** Three-component synthesis of indolo[2,3-*a*]quinolizines

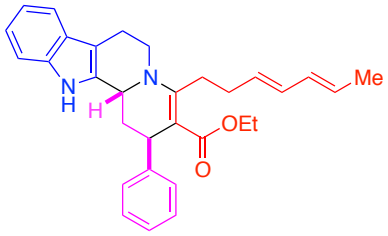
**Table 5.2:** Scope and yields of the synthesis of indolo[2,3-*a*]quinolizine derivatives

| Entry | Compd | $R^1$ | $R^2$ | $R^3$ | t (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **62** | Me | OEt | Ph | 1.5 | 86 |
| 2 | **63** | Me | OMe | Ph | 1 | 88 |
| 3 | **64** | Me | OEt |  | 1.5 | 86 |
| 4 | **65** | Me | OEt | 4-$ClC_6H_4$ | 1.5 | 88 |
| 5 | **66** | Me | OEt | 4-$MeOC_6H_4$ | 1.5 | 85 |
| 6 | **67** | Me | OEt | 2-$NO_2C_6H_4$ | 1.5 | 28 |
| 7 | **68** | Me | OEt |  | 1 | 77 |
| 8 | **69** | Me | OEt |  | 1 | 92 |
| 9 | **70** | Me | OEt | Me | 1 | 62 |
| 10 | **71** | Me | OEt | *n*-Pr | 1 | 40 |
| 11 | **72** | Me | S-$^t$Bu | Ph | 1 | 70 |
| 12 | **73** | Me | O-$^t$Bu | Ph | 1 | 68 |
| 13 | **74** | *n*-Pr | OEt | Ph | 1 | 50 |
| 14 | **75** | Me | Me | Ph | 1.5 | 48 |
| 15 | **75** | Me | Me | Ph | 12 | 72 |
| 16 | **75** | Me | Me | Ph | 2 | 80[a] |

[a] CAN (15 mol%) was used in this case

2-naphthyl (entry 8). Alkyl substituents at $R^3$ were also well tolerated (entries 9 and 10). While most experiments were performed on the

dicarbonyl substrate having $R^1$ = Me because of its commercial availability, longer alkyl chains were also tolerated, albeit in diminished yields. Thus, ethyl 3-oxohexanoate gave compound **74** in 50% yield (entry 13), and (*E*,*E*)-ethyl 3-oxo-6,8-decanedioate, prepared by a literature method based on dianion chemistry,[98] gave compound **76**, which bears a complex side chain containing a diene fragment, in 45% yield.




**76**

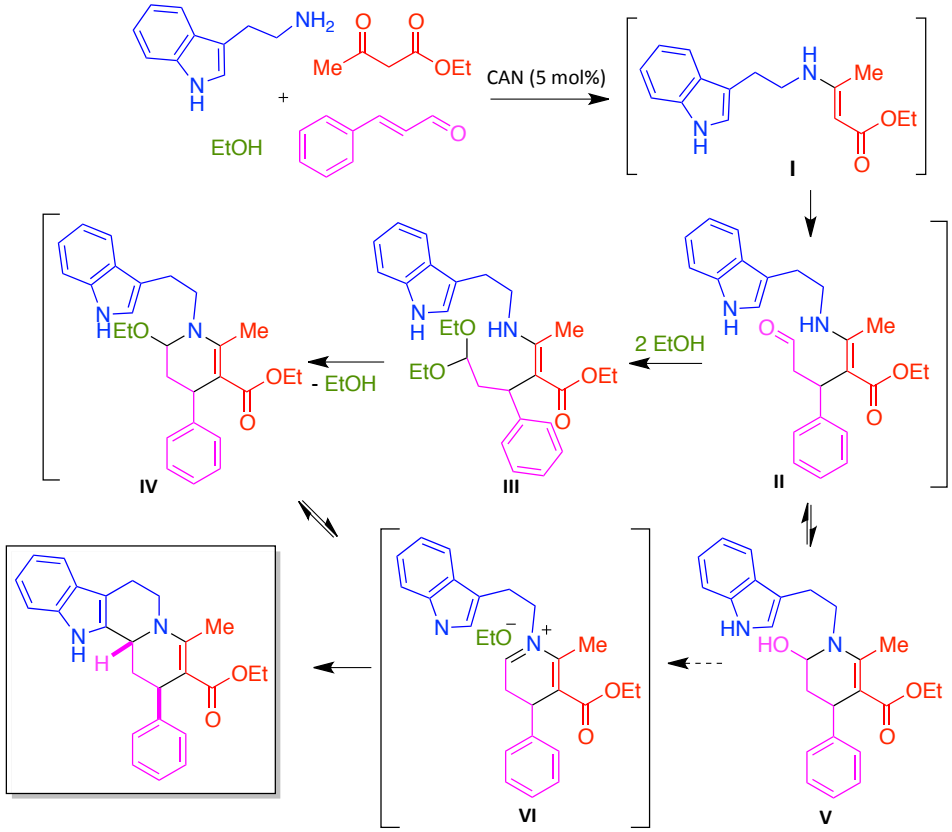
A plausible mechanistic pathway for the domino transformation is summarized in Scheme 5.3. We propose that the first step involves the formation of β-enaminone **I**, on the following basis: (a) CAN is an excellent catalyst for β-enaminone synthesis[99] and (b) in the synthesis of **62**, the use of the isolated β-enaminone arising from tryptamine and ethyl acetoacetate as starting material, together with cinnamaldehyde, led to an identical result as the multicomponent process using the same reaction conditions (84% yield in the presence of 5% CAN in ethanol, after 1 h reflux). Subsequent steps would involve a Michael addition of **I** to the unsaturated aldehyde to give **II**. Since we have verified that the reaction does not take place in the absence of ethanol, a role must be proposed for this reagent. CAN is able to catalyze the formation of acetals and related species,[100] and therefore we propose that a mechanistic possibility is that

98 Hiyama, T.; Morizawa, Y.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, 54, 2151.

99 Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Synlett* **2007**, 881.

100 (a) Manzo, E.; Barone, G.; Parrilli, M. *Synlett* **2000**, 887. (b) Roy, S. C.; Banerjee, B.

the next step involves the generation of **III**, which would then be cyclized to **IV**, a precursor to the vinylogous acyliminium cation **VI**. Finally, a Pictet-Spengler cyclization would afford the observed products. While it is concievable that **II** may experience a 6-*exo*-*trig* cyclization to the cyclic hemiaminal **V**, a potential precursor to cation **VI**, this pathway would not require the participation of ethanol, against the experimental observations. Furthermore, compounds related to intermediate **V** have been found to be unstable.[101]

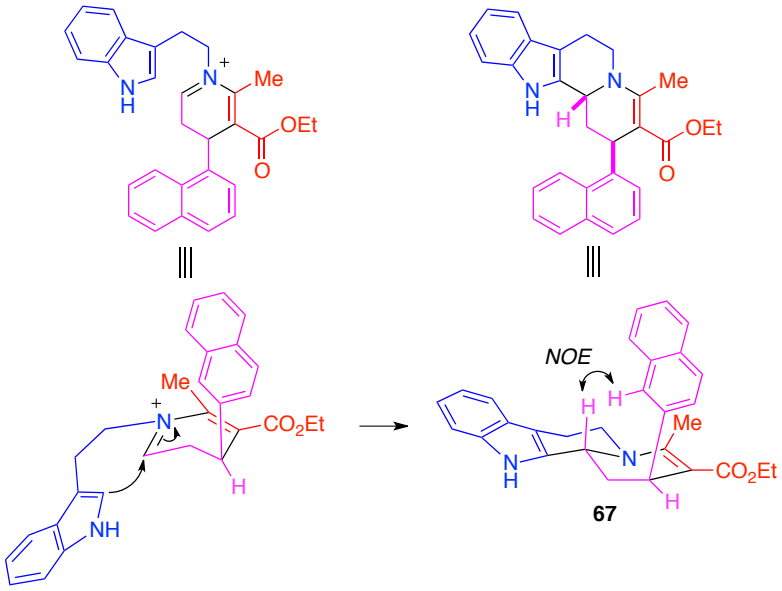



**Scheme 5.3**. Mechanism proposed to explain the formation of the indolo[2,3-*a*]quinolizine derivatives

*Synlett* **2002**, 1677. (c) Shindalkar, S. S.; Madje, B. R.; Hangarge, R. V.; Shingare, M. S. *Indian J. Chem.* **2005**, *44B*, 2409.

101 Sridharan, V.; Maiti, S.; Menéndez, J. C. *Chem. Eur. J.* **2009**, 15, 4565.

The stereochemistry of the reaction products was deduced from NOE studies on **69**, and was confirmed from the structure of their reduction derivatives (see below). As shown in Scheme 5.4, an NOE between the angular indoloquinolizine proton and H-2 at the naphthyl substituent proves their *cis* relationship. This product arises from attack of the indole ring to the vinylogous acyliminium intermediate opposite to the naphthyl substituent.

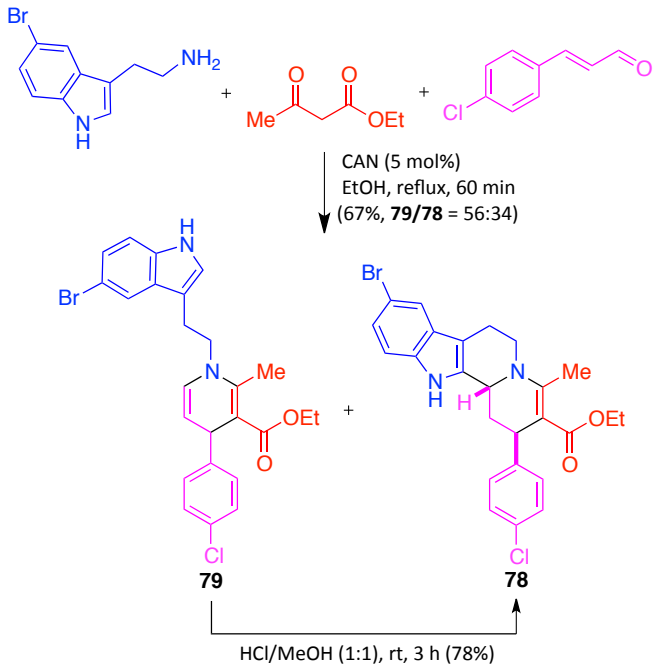



**Scheme 5.4**. Relative configuration of the indolo[2,3-*a*]quinolizine derivatives

At this stage, we became interested in verifying whether the reaction worked in the presence of less electron-rich aromatic side chains at the tryptamine component. To this end, we employed 5-bromotryptamine[102] as the starting material and found that its reaction with *p*-

102 For its synthesis, see: (a) Rad-Moghadam, K.; Sharifi-Kiasaraie, M.; Taheri-Amlashi, H. *Tetrahedron* **2010**, *66*, 2316. (b) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796. (c) Ito, T.; Kitajima, M.; Takayama, H. *Tetrahedron Lett*. **2009**, *50*, 4506.

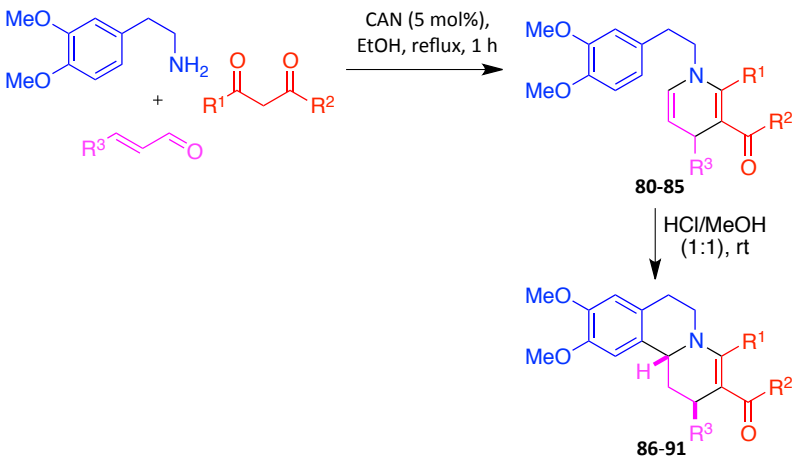
chlorocinnamaldehyde and ethyl acetoacetate afforded the desired compound **77** as the major product together with dihydropyridine **78**, which revealed that in this case an elimination reaction competed with the final Pictet-Spengler step. Fortunately, exposure of **78** to a 1:1 mixture of 35% aqueous HCl and methanol led to its transformation into the desired compound **77** in 78% yield (Scheme 5.5).




**Scheme 5.5**. Extension of the indolo[2,3-*a*]quinolizine synthesis to 5-bromotryptamine as substrate

## 5.3. SYNTHESIS OF BENZO[*a*]QUINOLIZINES

In order to further explore the synthetic scope of our domino process, we briefly investigated its application to the synthesis of benzo[*a*]quinolizines by use of 3,4-dimethoxyphenetylamine as the amine component. A behaviour similar to the one described for 5-bromotryptamine was observed, and the reaction products were identified as dihydropyridine derivatives **79**-**84**. As in the previous case, these compounds could be cyclized to the corresponding benzo[*a*]quinolizines **85**-**90** by treatment with a 1:1 mixture of 35% aqueous HCl and methanol at room temperature (Scheme 5.6 and Table 5.3) with the exception of the *tert*-butyl ester **80**, which, not unexpectedly, was unstable under these strongly acidic conditions.




**Scheme 5.6**. Synthesis of benzo[*a*]quinolizines

**Table 5.3:** Reaction conditions and yields for the synthesis of benzo[*a*]quinolizines

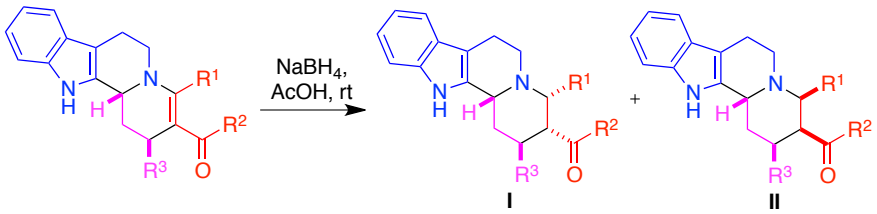
| Entry | $R^1$ | $R^2$ | $R^3$ | Dihydropyridines | | Benzo[*a*]quinolizines | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Cmpd. | Yield, %[a] | Cmpd. | Time, h | Yield, %[a] |
| 1 | Me | OEt | Ph | **79** | 70 | **85** | 2 | 75 |
| 2 | Me | O-$^t$Bu | Ph | **80** | 72 | **86** | 2 | 0[b] |
| 3 | Me | OEt | 4-$ClC_6H_4$ | **81** | 68 | **87** | 2 | 76 |
| 4 | Me | OEt | 4-$MeOC_6H_4$ | **82** | 65 | **88** | 4 | 77 |
| 5 | Me | OEt | Me | **83** | 62 | **89** | 8 | 63 |
| 6 | *n*-Pr | OEt | Ph | **84** | 60 | **90** | 2 | 60 |

[a]Yield of the isolated product, [b]Decomposition was observed in this case

## 5.4. SYNTHESIS AND STEREOCHEMICAL STUDY OF INDOLO[2,3-*a*]QUINOLIZIDINES AND BENZO[*a*]QUINOLIZIDINES

Finally, we examined the transformation of our indolo[2,3-*a*]quinolizines and benzo[*a*]quinolizines into the corresponding quinolizidine derivatives by reduction of their conjugated double bond in the presence of sodium triacetoxyborohydride, generated *in situ* from sodium borohydride and acetic acid.[103] This reagent is known to deliver two *cis* hydrogens to double bonds belonging to vinylogous amide systems such as those present in our substrates.[104]

The reduction of the indolo[2,3-*a*]quinolizines proceeded in good to excellent yields and afforded mixtures of the diastereomeric compounds **I** and **II** in *ca*. 40:60 ratios (Scheme 5.7 and Table 5.4). The major products were identified as the all-*cis* derivatives **II**, arising from reduction opposite to the $R^3$ substituent.

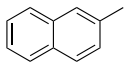



**Scheme 5.7**. Synthesis of indolo[2,3-*a*]quinolizidines

103 Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328.

104 Sridharan, V.; Menéndez, J. C. *Org. Lett.* **2008**, *10*, 4303.

**Table 5.4.** Results obtained in the synthesis of indolo[2,3-*a*]quinolizidines

| Entry | Compds (I,II) | $R^1$ | $R^2$ | $R^3$ | t (h) | Yield[a] (%) | I/II ratio[b] |
|---|---|---|---|---|---|---|---|
| 1 | **91**,**92** | Me | OEt | Ph | 2 | 86 | 40:60 |
| 2 | **93**,**94** | Me | OEt | 4-$PhC_6H_4$ | 5 | 85 | 46:54 |
| 3 | **95**,**96** | Me | OEt | 4-$ClC_6H_4$ | 2 | 89 | 40:60 |
| 4 | **97**,**98** | Me | OEt | 4-$MeOC_6H_4$ | 2 | 90 | 39:61 |
| 5 | **99**,**100** | Me | Me | Ph | 3 | 73[c] | 47:53 |
| 6 | **101**,**102** | Me | OEt |  | 3 | 80[c] | 39:61 |
| 7 | **103**,**104** | Me | S-$^t$Bu | Ph | 1.3 | 85 | 39:61 |
| 8 | **105**,**106** | Me | O-$^t$Bu | Ph | 1.3 | 80 | 48:52 |
| 9 | **107**,**108** | Me | OEt |  | 72[d] | 58[c] | 33:57 |
| 10 | **109**,**110** | Me | OEt | Me | 2 | 60[c] | 42:58 |
| 11 | **111**,**112** | Me | OEt | *n*-Pr | 2 | 68[c] | 40:60 |
| 12 | **113**,**114** | *n*-Pr | OEt | Ph | 36[e] | 65[c] | 35:65 |

[a]Yield of the isolated product. [b]Ratio calculated from $^1$HNMR spectra of the crude product. [c]Only one isomer could be isolated in pure form. [d]Starting material **69** (18%) was recovered. [e]Starting material **74** (22%) was recovered.

The relative configuration of diastereomers **I** and **II** was established from spectroscopic evidence, as summarized below for the representative cases of **91** and **92**. Arenoquinolizidines pose an interesting conformational problem owing to the presence of a bridgehead nitrogen atom that can be inverted, which complicates their stereochemical assignment.[105] The nitrogen lone pair and the proton at the quinolizidine ring fusion can be in *cis* and *trans* arrangements, which can be distinguished by several spectral criteria. Thus, compounds with a *trans* ring junction often show a characteristic series of IR bands between 2700 and 2800 $cm^{-1}$ known as

105 Avendaño, C.; Menéndez, J. C. in Jones, K. (ed.), Comprehensive Heterocyclic Chemistry III, vome 12, chapter 1 (Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. General Editors). Elsevier, Oxford, **2008**.

Bohlmann bands, which are absent in *cis* compounds and that are attributed to the stretching vibrations of the two C-H bonds antiperiplanar to the nitrogen lone pair.[106] These bands were present in the IR spectrum of the minor compound **91** (2799 $cm^{-1}$), but absent in that of **92**. The chemical shift of the ring junction proton in the $^{1}H$ NMR spectrum of quinolizidines also has diagnostic relevance, since its value depends on the dihedral angle between the C-H bond and the lone pair. A significant upfield shift has been found for the *trans*-fused systems ($\delta \approx 3.5$ ppm in the case of arenoquinolizidines) in comparison with their *cis* counterparts ($\delta >$ 4 ppm). In the case of compound **91**, this proton was observed at 3.79 ppm, which confirms the *trans* structure suggested by the IR data. Furthermore, the coupling constant values for the angular proton (11.2 and 1.0 Hz) were compatibe only with a *trans* fusion, which leads to a large diaxial coupling. The $^{1}H$ NMR spectrum of compound **92** showed the fusion proton H-12b at $\delta$ = 4.86 ppm, as a triplet with $J$ = 2.6 Hz, which is consistent with a *cis* quinolizidine structure. NOE data were used to confirm the proposed relative configurations (Figure 5.3), which were also supported by the coupling constants for the $H_1$-$H_4$ protons.

*Trans*-arenoquinolizidines are usually considered to be thermodinamically more stable than their *cis* counterparts because of their all-equatorial framework. However, the tendency of compound **92** to exist in a *cis* form can be easily explained by the repulsion between the phenyl and methyl substituents in a hypotethical *trans* compound, which would become *cis* by chair flipping accompanied by inversion of the angular nitrogen. Fascinatingly, the *cis* fusion in compound **92** is associated to a much higher

106 Wolfe, S.; Schlegel, H. B.; Whangbo, M.-H. *Can. J. Chem*. **1974**, *52*, 3787.

polarity in comparison with its isomer **91**, which can be explained by the better accesibility of their nitrogen lone pair.

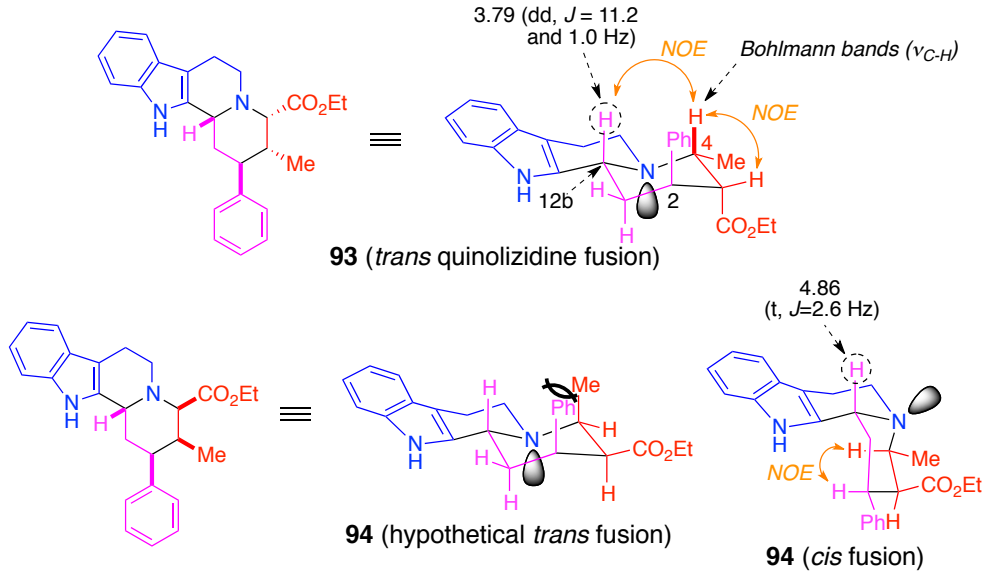
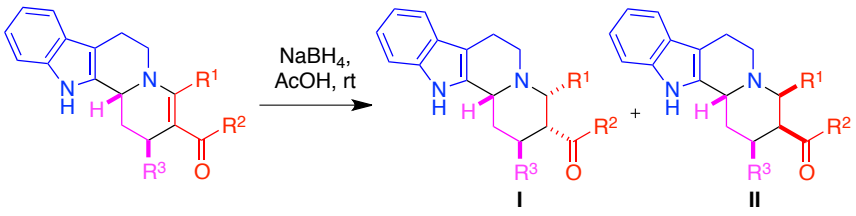



**Figure 5.3**. Stereochemical study of compounds **91** and **92**

The reduction of benzo[*a*]quinolizine derivatives was also studied, and found to afford benzo[*a*]quinolizidines **III** and **IV** under similar conditions to the indoloquinolizine case. Again, the major products were compounds **II**, arising from the formal delivery of hydrogen opposite to the $R^3$ substituent (Scheme 5.8 and Table 5.5).



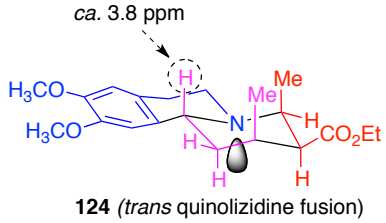

**Scheme 5.8**. Synthesis of benzo[*a*]quinolizidines

**Table 5.5.** Results obtained in the synthesis of benzo[*a*]quinolizidines

| Entry | Compds (III,IV) | $R^1$ | $R^2$ | $R^3$ | Yield[a] (%) | III/IV ratio[b] |
|---|---|---|---|---|---|---|
| 1 | **115,116** | Me | OEt | Ph | 90[c] | 38:62 |
| 2 | **117,118** | Me | OEt | *p*-$ClC_6H_4$ | 92 | 35:65 |
| 3 | **119,120** | Me | OEt | *p*-$MeOC_6H_4$ | 82[c] | 32:68 |
| 4 | **121,122** | *n*-Pr | OEt | Ph | 78[d] | 35:65 |
| 5 | **123,124** | Me | OEt | Me | 79[c] | 35:65 |

[a]Yield of the isolated product. [b]Ratio calculated from $^1$HNMR spectra of the crude product. [c]only one isomer could be isolated in pure form

While compounds **III** and **IV** showed the same spectral characteristics as the corresponding indoloquinolizidines, it is interesting to remark that the benzo[*a*]quinolizidines bearing a methyl substituent at C-2 (compounds **123** and **124**) showed a peculiar conformational behavior. Thus, in this case the major product **124** can be assumed to have a *trans* quinolizidine fusion, since the angular 11b proton is hidden inside a multiplet at *ca*. 3.8 ppm instead of appearing at *ca.* 4.6 ppm, as in the case of the corresponding indoloquinolizidines (Figure 5.4). This difference can be ascribed to a less unfavourable 1,3-diaxial interaction between the two methyl substituents at C-2 and C-4 in **124**, in comparison with the one between a methyl and an aryl substituent in all the other cases.




**124** (*trans* quinolizidine fusion)

**Figure 5.4**. Preferred conformation of compound **124**

# 6. Synthesis of piperidines based on a multicomponent reaction

## 6.1. INTRODUCTION

A large number of biologically active natural products are piperidine derivatives,[107] and in fact about 50% of known alkaloids contain a piperidine substructure.[108] Some representative piperidine alkaloids include pseudoconhydrine, which shows antispasmodic properties,[109] sedamine,[110] solenopsin A, found in plants but also in the animal kingdom, specially in insects,[111] and which inhibits angiogenesis via the phosphoinositol-3-kinase (Pl3-K) pathway and exhibits cytotoxic, insecticidal, antibacterial, antifungal and anti-HIV properties.[112]

107 For selected reviews and monographs on piperidine alkaloids, see: (a) Fodor, G. B.; Colasanti, B. "The Pyridine and Piperidine Alkaloids: Chemistry and Pharmacology" in The Alkaloids: Chemical and Biological Perspectives (Ed.: Pelletier, S. W.), Pergamon, Oxford, 1975, vol. **3**, p. 1. (b) Strunz, G. M.; Findlay, J. A. The Alkaloids; Brossi, A. Ed.; Academic: New York, 1985, vol. **26**, p. 89. (c) Comins, D. L.; Joseph, S. P. In Advances in Nitrogen Heterocycles, vol. 2 (Ed.: C. J. Moody), JAI Press, Greenwich C. T. **1996**, pp. 251. (d) O'Hagan, D. *Nat. Prod. Rep*. 2000, ***17***, 435. (e) Toyooka, N.; Nemoto, H. in Studies in Natural Products Chemistry, vol. 29 (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam (The Netherlands), **2003**, pp. 491.

108 Amat, M.; Pérez, M.; Bosch, J. *Synlett* **2011**, 143.

109 Brown, E.; Lavoue, J.; Dhal, R. *Tetrahedron* **1973**, *29*, 455.

110 Bates, R. W.; Boonsombat, J. *Org. Biomol. Chem.* 2005, *3*, 520.

111 Fodor, G. B.; Colasanti, B. Alkaloids: Chemical and Biological Perspectives, Wiley: New York, **1985**, Vol. 3.

112 (a) Koch, R. B.; Desaiah, D.; Foster, D.; Ahmed, K. *Biochem. Pharmacol*. **1977**, *26*, 983. (b) Howell, G.; Butler, J.; DeShazo, R. D.; Farley, J. M.; Liu, H.-L.; Nanayakkara, N. P. D.; Yates, A.; Yi, G. B.; Rockhold, R. W.; *Ann. Allergy. Asthma. Immunol*. **2005**, *94*, 380. (c) Girard, N.; Hurvois, J.-P. *Synth. Commun*. **2005**, *35*, 711.

Deoxoprosopinine has antibiotic and anaesthetic properties,[113] and nojirimycin,[114] a representative of carbohydrate-like alkaloids or imino sugars, is an inhibitors of glycosidases and glycosyltransferases. N-Methylanabasine, an analogue of nicotine, is one of the alkaloids found in the tobacco plant (figure 6.1).[115] Finally, some piperidine alkaloids are potent poisons, including the neurotoxins β-conhydrine[116] and coniine, a neuromuscular blocker from hemlock (*Conium maculatum*), a plant that has been known as a poison since antiquity and was used in ancient Greece to execute condemned prisoners, including the philosopher Socrates in 399 B.C.

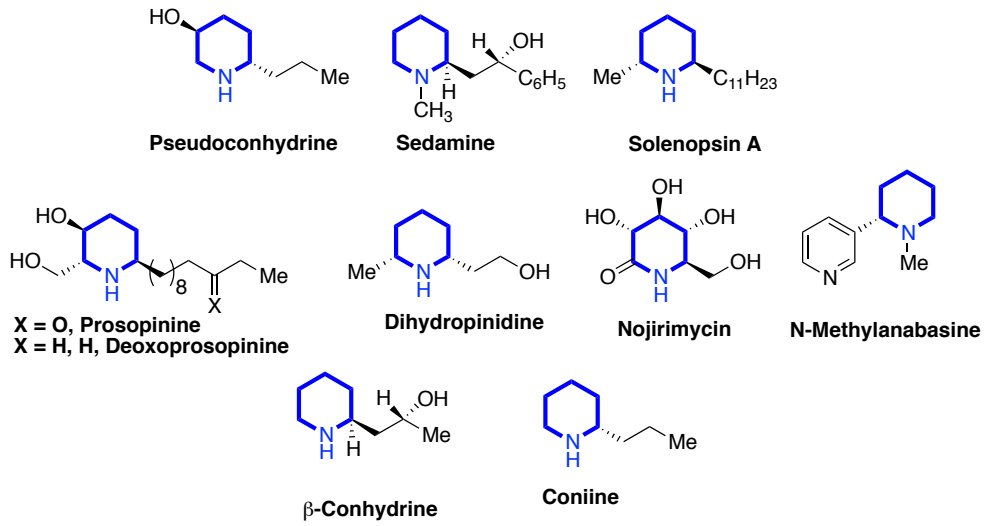



**Figure 6.1**. Some bioactive piperidine alkaloids

There is also a large number of number of bioactive synthetic piperidine derivatives, many of which are drugs employed in therapeutics. For

113 (a) Wang, Q.; Sasaki, N. A. *J. Org. Chem*. **2004**, 69, 4767. (b) Fuhshuku, K.-I.; Mori, K. *Tetrahedron: Asymmetry* **2007**, 18, 2104.

114 Bruce, I.; Fleet, G. W. J.; Bello, I. C.; Winchester, B. *Tetrahedron Lett.* **1989**, 30, 7257.

115 Felpin, F. X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villieras, J.; Lebreton, J. *J. Org. Chem*. **2001**, 66, 6305.

116 Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem*. **2007**, 72, 5358.

example (figure 6.2), paroxetine[117] is a member of the selective serotonin reuptake inhibitor (SSRI) class of antidepressant drugs, ethylphenidate[118] is a psychostimulant drug used for the treatment of attention-deficit hyperactivity disorder (ADHD), postural orthostatic tachycardia syndrome and narcoepsy. Pipradrol[119] and desoxypipradrol[120] are employed as stimulants acting as norepinephrine-dopamine reuptake inhibitors (NDRI). Pethidine (meperidine)[121] is an opioid analgesic drug, risperidone[122] and haloperidol[123] are potent antipsychotic drugs used for the treatment of schizophrenia, and acting as a dopamine inverse agonists, and minoxidil[124] is an vasodilator drug used initially as antihypertensive and more recently for the treatment of androgenic alopecia.

Due to their importance, the literature describes many methologies for the synthesis of substituted piperidines.[125] These methods allow access to a

117 (a) Serretti, A.; Zanardi, R.; Cusin, C.; Rossini, D.; Lorenzi, C.; Smeraldi, E. *Eur. Neuropsychopharmacol* **2001**, 11, 5, 375. (b) Rakofsky, J. J.; Holtzheimer, P. E.; Nemeroff, C. B. *Curr. Opin. Chem. Biol.* **2009**, 13, 3, 291.

118 Patrick, K. S.; Williard, R. L.; VanWert, A. L.; Dowd, J. J.; Oatis, J. E. Jr.; Middaugh, L. D. *J. Med. Chem.* **2005**, *48*, 2876.

119 Davidson, C.; Ramsey, J. *J. Psychopharmacol.* **2012**, *26*, 1036.

120 Coppola, M.; Mondola, R. *Toxicol. Lett*. **2012**, *1*, 57.

121 Hashemi, S. J.; Soltani, H.; Heidari, S. M.; Rezakohanfekr, M. *Adv. Biomed. Res.* **2013**, *2*, 9.

122 Suzuki, H.; Inoue, Y.; Gen. K. *Ther. Adv. Psychopharmacol.,* **2012**, *6*, 227.

123 Donnelly, L.; Rathbone, J.; Adams, C. E. *Cochrane Database Syst. Rev.* **2013**, Aug 28, 8.

124 Bhatti, H. A.; Basra, M. K.; Patel, G. K. *J. Cosmet. Dermathol.* **2013**, *12*, 223.

125 For selected reviews of piperidine synthesis, see: (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.,* **1998,** 633. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem*. **2003**, 3693. (c) Borcherding, D. R.; Kane, J. M.; Sabol, J. S.; Weintraub, P. M. *Tetrahedron,* **2003**, *59*, 2953. (d) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (e) Pearson, M. S. M.; Mathe-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem*. **2005**, 2159. (f) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem*. **2005**, *3*, 1349. (g) Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198. (h) Källström, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601.

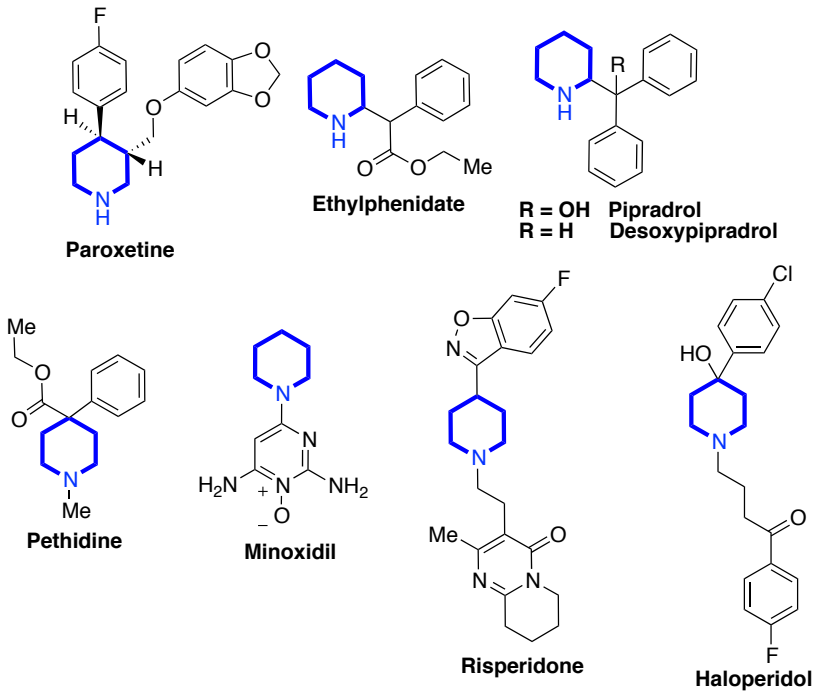



**Figure 6.2**. Some drug molecules containing piperidine substructures

variety of substitution patterns, including 2-substituted,[126] 2,3-disubstituted,[127] 2,5-disubstituted,[128] 2,6-disubstituted,[129] 3,4-

126 For representative examples, see: (a) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, 127, 8966. (b) Jamieson, A. G.; Sutherland, A. *Org. Lett.* **2007**, 9, 8, 1609. (c) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Lett.* **2007**, 9, 13, 2473. (d) Mukherjee, P.; Widenhoefer, R. A. *Org. Lett.* **2011**, 13, 6, 1334.

127 For representative examples, see: (a) Noel, R.; Vanucci-Bacque, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *Eur. J. Org. Chem.* **2007**, 476. (b) Garrido, N. M.; García, M.; Díez, D.; Sánchez, M. R.; Sanz, F.; Urones, J. G. *Org. Lett.* **2008**, 10, 9, 1687. (c) Ahari, M.; Pérez, A.; Menant, C.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2008**, 10, 12, 2473.

128 For representative examples, see: (a) Desai, M. C. Stephens Stramiello, L. M. *Tetrahedron Lett.* **1993**, 34, 48, 7685. (b) Varea, T.; Dufour, M.; Micouin, L.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1995**, 36, 7, 1035. (c) Macchia, B.; Macchia, M.; Martinelli, A.; Martinotii, E.; Orlandini, E.; Romagnoli, F.; Scatizzi, R. *Eur. J. Med. Chem.* **1997**, 32, 231. (d) Larivee, A.; Charette, A. B. *Org. Lett.* **2006**, 8, 18, 3955.

129 For representative examples, see: (a) Kubizna, P.; Spanik, I.; Lozisek, J.; Szolcsanyi, P. *Tetrahedron* **2010**, 66, 2351. (b) Coia, N.; Mokhtari, N.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2011**, *13*, 6292. (c) Radha-Krishna, P.; Reddy, B. K. *Tetrahedron: Asymmetry* **2013**, *24*, 758.

disubstituted,[130] 2,3,6-trisubstituted,[131] 2,4,5-trisubstituted[132] and polysubstituted[133] piperidine derivatives. Representative examples of the types of structures currently amenable to synthesis are summarized in Figures 6.3 and 6.4.

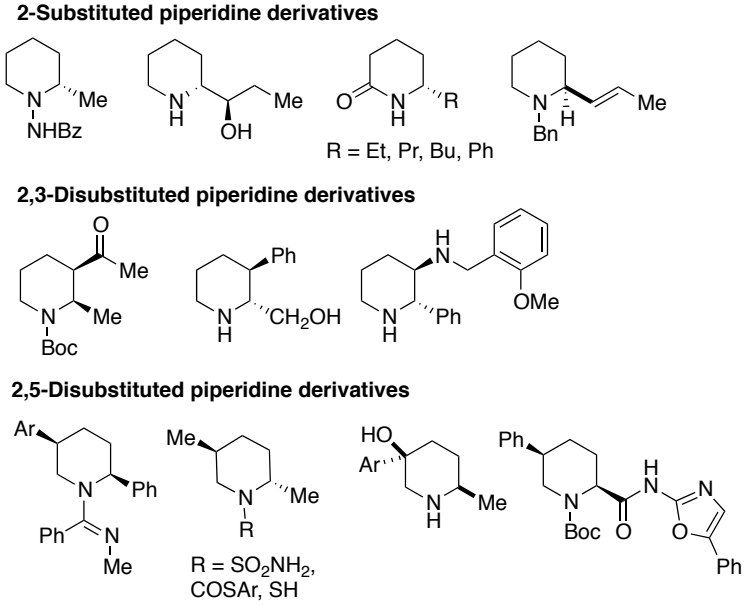



**Figure 6.3**. Some substitution patterns available through known synthetic approaches to piperidine

130 For a review, see: De Risi, C.; Fanton, G.; Pollini, G. P.; Trapella, C.; Valente, F.; Zanirato, V. *Tetrahedron: Asymmetry* **2008**, *19*, 131.

131 For representative examples, see: (a) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747. (b) Moustafa, M. M. A. R.; Pagenkopf, B. L. *Org. Lett*. **2010**, *12*, 4732. (c) Arena, G.; Zill, N.; Salvadori, J.; Girard, N.; Mann. A.; Taddei, M. *Org. Lett.* **2011**, *13*, 2294.

132 For representative examples, see: (a) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743. (b) Heretsch, P.; Rabe, S.; Giannis, A. *Org. Lett.* **2009**, *11*, 5410.

133 For representative examples, see: (a) Boglio, C.; Stahlke, S.; Thorimbert, S.; Malacria, M. *Org. Lett.* **2005**, *7*, 4851. (b) Muthusamy, S.; Krishnamurthi, J.; Suresh, E. *Org. Lett.* **2006**, *8*, 5101. (c) Chen, Y.; Zhong, C.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *Org. Lett.* **2009**, *11*, 2333. (d) Han, B.; Xiao, Y.-C.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2009**, *11*, 4660. (e) Imashiro, R.; Uehara, H.; Barbas lll, C. F. *Org. Lett.* **2010**, *12*, 5250. (f) Urushima, T.; Sakamoto, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12*, 4588. (g) Wang, Y.; Zhu, S.; Ma, D. *Org. Lett.* **2011**, *13*, 1602.

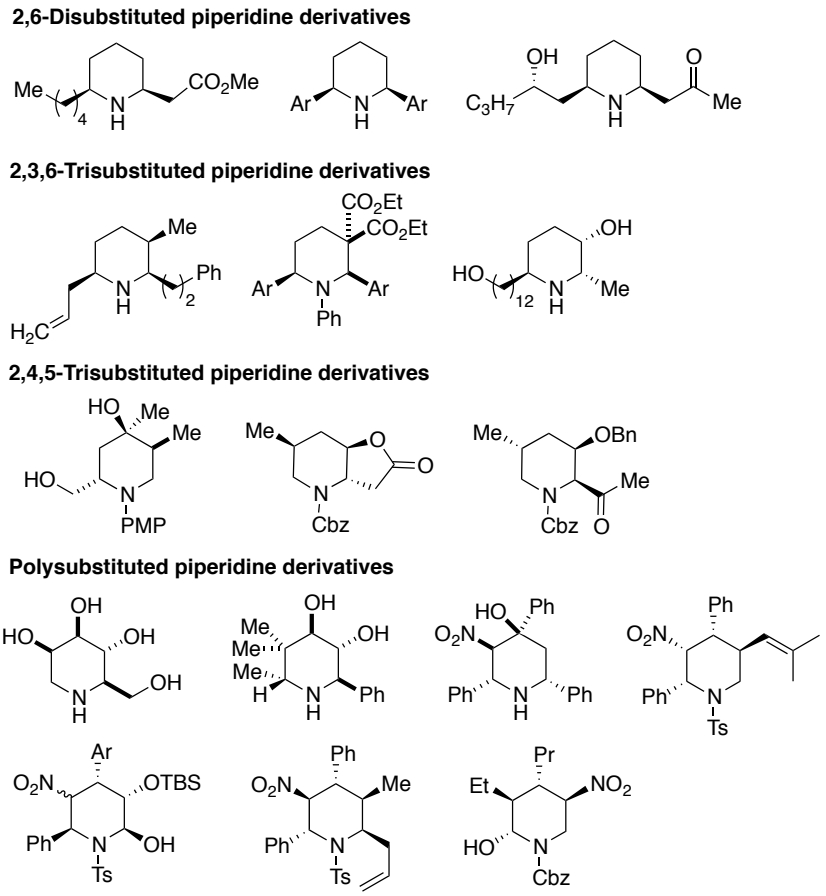
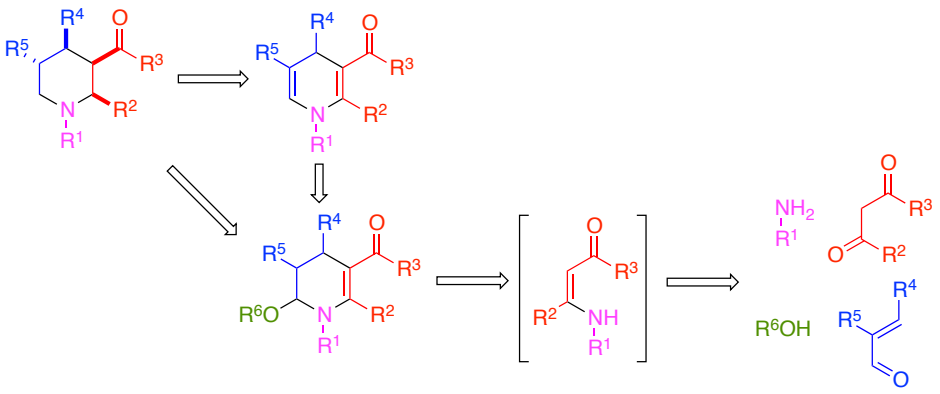



**Figure 6.4**. Some substitution patterns available through known synthetic approaches to piperidine

Based on the multicomponent tetrahydropyridine synthesis developed by our group[134] and used as the basis for our routes to indoloquinolizine and benzoquinolizine derivatives described in the previous chapter, we have developed a general, diastereoselective, two-step synthesis of polysubstituted piperidine derivatives from readily available, simple starting materials through β-enamino ester intermediates, as summarized in Scheme 6.1.

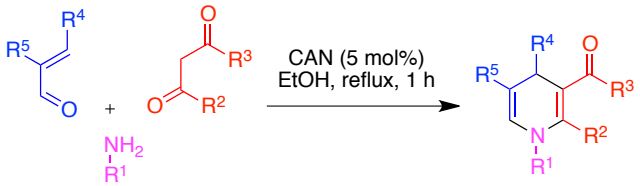
134 (a) Sridharan, V.; Maiti, S.; Menéndez, J. C. *Chem. Eur. J.* **2009**, *15*, 4565. (b) Sridharan, V.; Maiti, S.; Menéndez, J. C. *J. Org. Chem*. **2009**, *74*, 9365.




**Scheme 6.1**. Planning of piperidine synthesis

## 6.2. SYNTHESIS OF STARTING MATERIALS

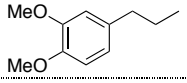
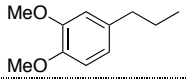
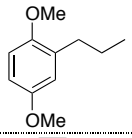
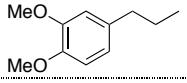
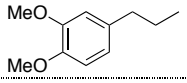
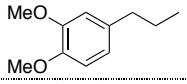
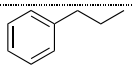
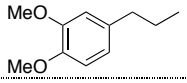
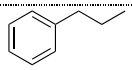
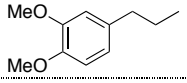
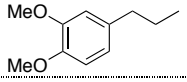
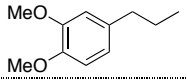
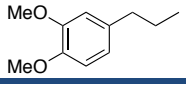
As previously mentioned, the multicomponent reaction between primary amines, α,β-unsaturated aldehydes, β-dicarbonyl compounds and alcohols affords initially 6-alkoxy-1,4,5,6-tetrahydropyridine derivatives. As shown by other members of our group, these compounds can be transformed into 1,4-dihydropyridines in refluxing ethanol or acetonitrile containing suspended neutral alumina (activity grade I).[135] This protocol has the disadvantage of requiring a separate operation to separate the final products from the alumina, which requires repeated washes with polar solvents, under heating. In the present thesis we have improved this method simply by carrying out the multicomponent reaction in refluxing ethanol. This different behaviour suggests that, under these conditions in which the 6-alkoxy-1,4,5,6-tetrahydropyridine are not isolated, the elimination reaction takes place on a different species, probably the 6-hydroxy derivative generated in the previous step of the mechanism (Scheme 6.2). As shown in Table 6.1, the method was quite general and allowed the preparation of dihydropyridines with a variety of aliphatic or aromatic substituents at $R^1$ and $R^4$, but was restricted to small alkyl substituents at $R^2$ and $R^5$ (mainly because of the limited range of commercial starting materials available), and ester groups at $R^3$.



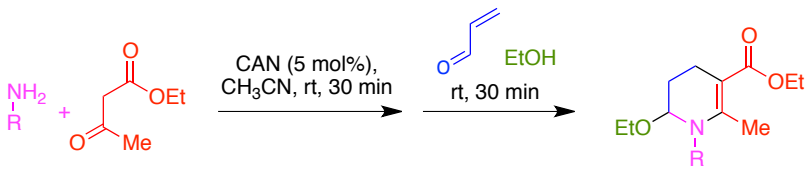

**Scheme 6.2**. Three-component synthesis of dihydropyridines

135 (a) Maiti, S.; Menéndez, J. *Synlett* **2009**, 2249. (b) Maiti, S.; Sridharan, V.; Menéndez, J. C. *J. Comb. Chem.* **2010**, *12*, 713.

**Table 6.1**. Results obtained in the synthesis of dihydropyridine derivatives

| Entry | Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **79** |  | Me | OEt | Ph | H | 70 |
| 2 | **80** |  | Me | O-$^t$Bu | Ph | H | 72 |
| 3 | **125** |  | Me | OEt | Ph | H | 66 |
| 4 | **126** |  | Me | OEt | Ph | H | 66 |
| 5 | **84** |  | *n*-Pr | OEt | Ph | H | 60 |
| 6 | **127** |  | Me | OEt | *p*-$MeC_6H_4$ | H | 62 |
| 7 | **82** |  | Me | OEt | *p*-$MeOC_6H_4$ | H | 65 |
| 8 | **128** |  | Me | OEt | *p*-$MeOC_6H_4$ | H | 68 |
| 9 | **129** | *n*-Pr | Me | O-$^t$Bu | *p*-$NO_2C_6H_4$ | H | 70 |
| 10 | **130** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H | 78 |
| 11 | **131** | Bn | Me | OEt | *p*-$NO_2C_6H_4$ | H | 72 |
| 12 | **132** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H | 86 |
| 13 | **133** | *n*-Bu | Me | OEt | *o*-$NO_2C_6H_4$ | H | 68 |
| 14 | **81** |  | Me | OEt | *p*-$ClC_6H_4$ | H | 68 |
| 15 | **134** |  | Me | OEt | Et | Me | 64 |
| 16 | **83** |  | Me | OEt | Me | H | 62 |
| 17 | **135** | Bn | Me | OEt | Me | H | 55 |
| 18 | **136** | *n*-Pr | Me | OEt | Me | H | 68 |
| 19 | **137** | *n*-Bu | Me | OEt | Me | H | 65 |
| 20 | **138** |  | Me | OEt | H | Me | 53 |

We also studied the reduction of a few representative 6-alkoxy-1,4,5,6-tetrahydropyridines, which are summarized in Figure 6.5. Compounds **139**-**141** were known in the literature,[134a] and **143** and **144** had to be used in crude state beacause all attempts at their purification led to their decomposition. These materials were prepared by our previuosly described method, involving a sequential four-component reaction at room temperatura (Scheme 6.3).[134a]




**Scheme 6.3**. Four-component synthesis of 6-ethoxy-1,4,5,6-tetrahydropyridines

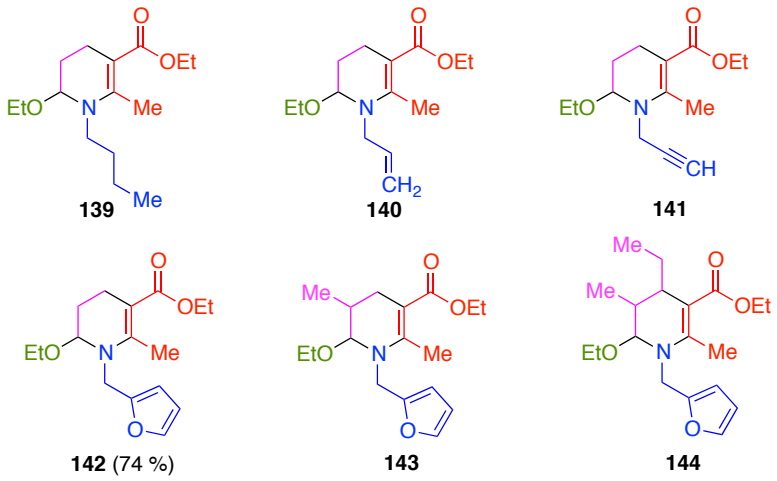
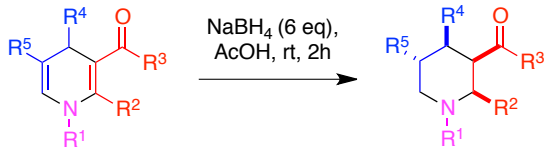



**Figure 6.5**. 6-Alkoxy-1,4,5,6-tetrahydropyridines selected for reduction studies

## 6.3. PIPERIDINE SYNTHESIS

For the synthesis of piperidine derivatives, we exposed the corresponding 1,4-dihydropyridines to sodiumtriacetoxyborohydride, $Na(OAc)_3BH$, (STAB), a mild reducing reagent in which the electron-withdrawing effects of the three acetoxy groups stabilize the boron-hydrogen bond.[136] Following a protocol previously used by our group,[137] STAB was generated *in situ* from sodium borohydride and acetic acid at room temperature. The reduction of our dihydropyridine substrates proceeded with complete diastereoselectivity, affording the target piperidines as a single diasteroisomer in a one-pot procedure. With this method we were able to synthesize a broad range of piperidine derivatives bearing up to five substituents including a variety of aliphatic or aromatic substituents at $R^1$ and $R^4$, small alkyl substituents at $R^2$ and $R^5$, and ester groups at $R^3$ (Scheme 6.4). Furthermore, the mild reduction conditions were compatible with several functional groups, including ester, nitro, ether and chloro. As shown in table 6.2, the yields were quite satisfactory and normally laid in the 75-90% range.

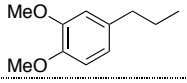
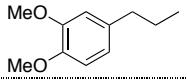
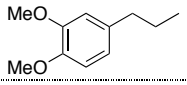
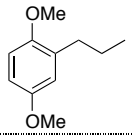
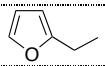
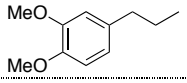
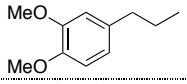
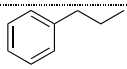
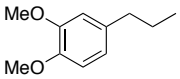
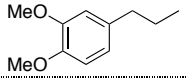
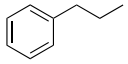
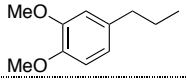
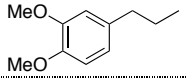
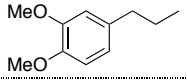



**Scheme 6.4**. Synthesis of piperidines by reduction of 1,4-dihydropyridines

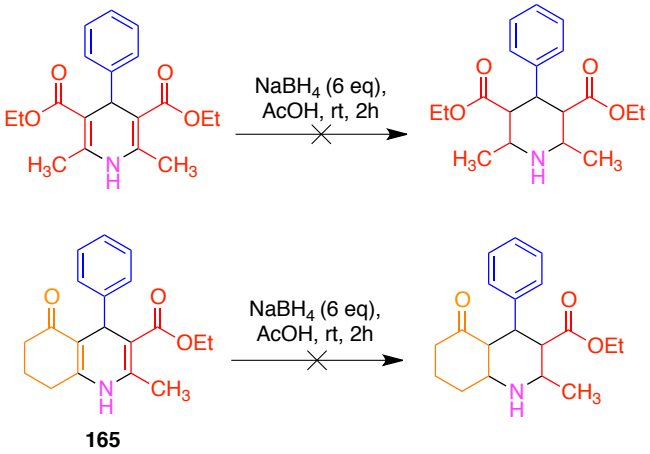
136 For reviews of sodium triacetoxyborohydride as a reducing agent, see: (a) Abdel-Magid, A.; Mehrman, S. J. *Org. Proc. Res. Devel.* **2006**, 10, 971. (b) Gribble, G. W. *Chem. Soc. Rev.* **1998**, 27, 395.

137 For precedents of the use of sodium triacetoxyborohydride for the reduction of endocyclic vinyl carbamate bonds, see: (a) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328. (b) Sridharan, V.; Menéndez, J. C. *Org. Lett*. **2008**, *10*, 4303.

**Table 6.2**. Results obtained in the reduction of dihydropyridine derivatives with STAB

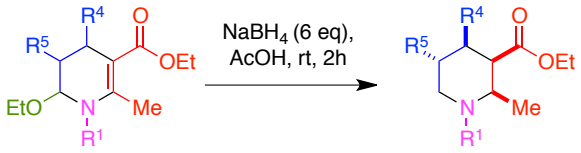
| Entry | Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **145** |  | Me | OEt | Ph | H | 88 |
| 2 | **146** |  | *n*-Pr | OEt | Ph | H | 79 |
| 3 | **147** |  | Me | O-$^t$Bu | Ph | H | 84 |
| 4 | **148** |  | Me | OEt | Ph | H | 78 |
| 5 | **149** |  | Me | OEt | Ph | H | 92 |
| 6 | **150** |  | Me | OEt | *p*-$MeC_6H_4$ | H | 78 |
| 7 | **151** |  | Me | OEt | *p*-$MeOC_6H_4$ | H | 71 |
| 8 | **152** |  | Me | OEt | *p*-$MeOC_6H_4$ | H | 68 |
| 9 | **153** |  | Me | OEt | *p*-$ClC_6H_4$ | H | 90 |
| 10 | **154** | Bn | Me | OEt | *p*-$NO_2C_6H_4$ | H | 78 |
| 11 | **155** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H | 87 |
| 12 | **156** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H | 86 |
| 13 | **157** | *n*-Pr | Me | O-$^t$Bu | *p*-$NO_2C_6H_4$ | H | 82 |
| 14 | **158** | *n*-Bu | Me | OEt | *o*-$NO_2C_6H_4$ | H | 79 |
| 15 | **159** |  | Me | OEt | Et | Me | 62 |
| 16 | **160** |  | Me | OEt | Me | H | 75 |
| 17 | **161** | Bn | Me | OEt | Me | H | 77 |
| 18 | **162** |  | Me | OEt | H | Me | 67 |
| 19 | **163** | *n*-Pr | Me | OEt | Me | H | 72 |
| 20 | **164** | *n*-Bu | Me | OEt | Me | H | 76 |

We also examined briefly the reduction of two dihydropyridine derivatives in which both double bonds belong to vinylogous amide or carbamate substructures, including a typical Hantzsch dihydropyridine[138] and octahydroquinolin-5-one derivative **165**, prepared by another member of our group.[139] Both experiments failed (Scheme 6.5), suggesting that in these cases the electron density at the dihydropyridine nitrogen is not enough to trigger the initial protonation event (see the mechanistic discussion below).




**Scheme 6.5**. Failed reduction of doubly conjugated 1,4-dihydropyridines with STAB

Finally, we also examined the reduction of a few representative 6-alkoxy-1,4,5,6-tetrahydropyridines, obtaining identical results as those described for the dihydropyridines (Scheme 6.6 and table 6.3).




**Scheme 6.6**. Reduction of 6-alkoxy-1,4,5,6-tetrahydropyridines with STAB

138 Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. *Tetrahedron Lett*. **2005**, *46*, 5771.
139 Raja, V. P. A.; Menéndez, J. C. Unpublished results.

**Table 6.3**. Results obtained in the reduction of 6-alkoxy-1,4,5,6-tetrahydropyridine derivatives with STAB

| Entry | Compds | $R^1$ | $R^4$ | $R^5$ | Yield (%) |
|---|---|---|---|---|---|
| 1 | **166** | $H_2C$=CH-$CH_2$- | H | H | 78 |
| 2 | **167** | HC≡C-$CH_2$- | H | H | 75 |
| 3 | **168** |  | H | Me | 82 |
| 4 | **169** |  | Et | Me | 71 |
| 5 | **170** |  | H | H | 90 |
| 6 | **171** | *n*-Bu- | H | H | 80 |

The stereochemistry of piperidine derivatives was studied on compound **169**, for which the signals of all key protons are sufficiently separated to allow meaningful NOE experiments, which are summarized in Figure 6.6. These data show an all-*cis* relative configuration for the substituents at C-2, C-3 and C-4, with the one at C-5 being *trans* with respect to the others. In this structure, all substituents are equatorial except the ester group at C-3, which is axial.

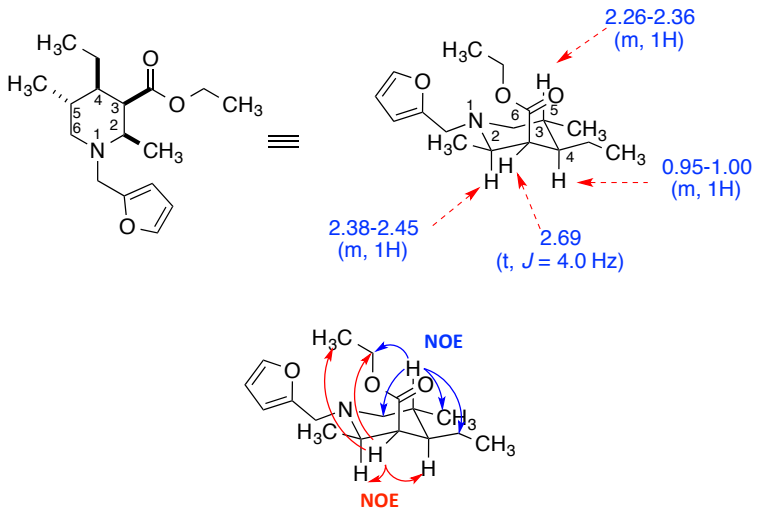
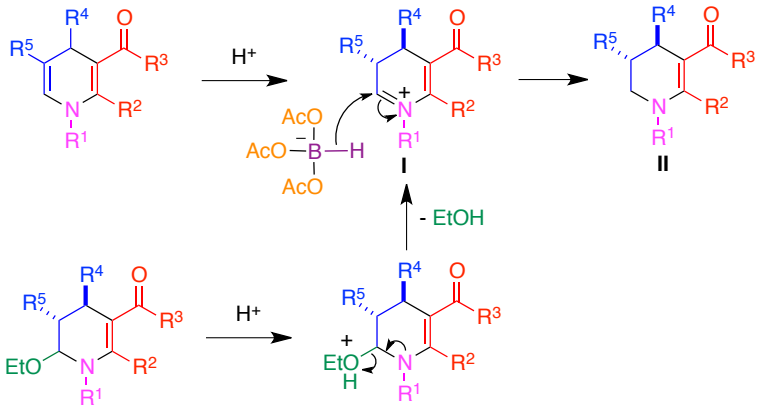



**Figure 6.6**. Key $^1$H-NMR signals and NOEs of compound **169**

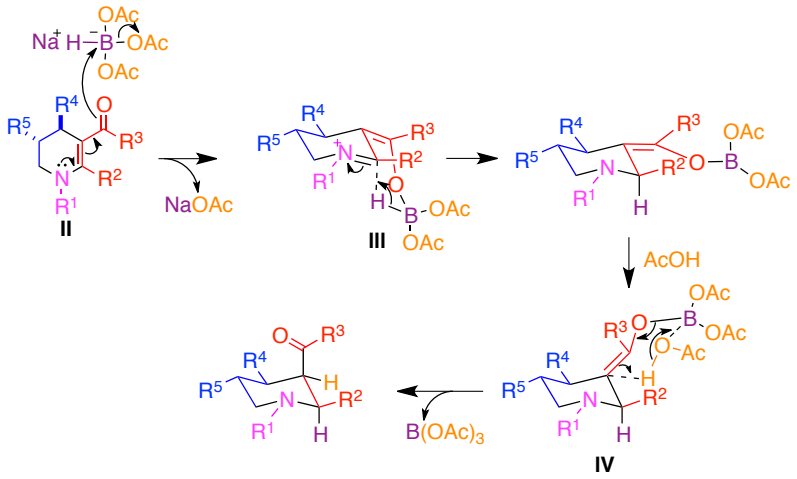
Mechanistically, the dihydropyridine reduction can be proposed to start by the generation of a vinylogous acyliminium species **I** *via* protonation of the C5-C6 double bond of the starting dihydropyridine, which is more nucleophlilic because of the absence of an electron-withdrawing group. This protonation takes place in such a way that the $R^4$ and $R^5$ substituents end up in equatorial position, and therefore in a *trans* arrangement. In the reactions strating from 6-alkoxy-1,4,5,6-tetrahydropyridines, the same intermediate (**I**) is reached by protonation of the 6-ethoxy substituent and loss of a molecule of ethanol. Reduction of the iminium group in **I** by the hydride donor affords intermediate **II** (Scheme 6.7).




**Scheme 6.7**. Initial stages of the reduction of 1,4-dihydropyridines and 6-alkoxy-1,4,5,6-tetrahydropyridines by STAB

In subsequent stages, sodium triacetoxyborohydride reduces the C=C double bond of the vinylic carbamate group present in **II**. This reagent is known to deliver two hydrogen atoms from the same face of the double bond,[137a] according to the mechanism summarized in Scheme 6.8 that involves an initial coordination of the ester carbonyl oxygen with boron (**III**), followed by intermolecular hydride transfer onto the resulting iminium cation to generate intermediate **IV**, with an equatorial $R^2$

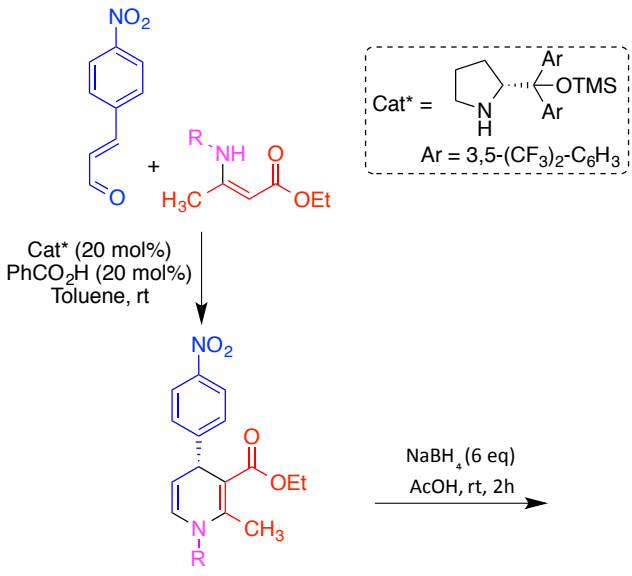
substituent. The final step involves attack of the boron enolate to a molecule of acetic acid, and affords the final product with loss of a molecule of boron triacetate.




**Scheme 6.8**. Final stages of the reduction of 1,4-dihydropyridines and 6-alkoxy-1,4,5,6-tetrahydropyridines by STAB

We finally examined the integrity of the stereocenters during the STAB reduction. To this end, we prepared chiral dihydropyridines using an organocatalytic method reported while our work was in progress,[140] based on the reaction between β-enaminones and cinnamaldehyde derivatives in the presence of the Hayashi-Jørgensen catalyst and benzoic acid. Using this method, we prepared compounds **172** and **173**, in 89 and 83% enantiomeric excess, respectively. The application of our reduction protocol to these materials afforded piperidines **174** and **175**, which we isolated in 84% and 83% ee, respectively (Scheme 6.9). We conclude, therefore, that the STAB reduction does not have a significant effect on the integrity of the stereocenters present in the piperidine ring.

140 Noole, A.; Borissova, M.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2011**, *76*, 1538.




| Compound | R | Yield, % | ee, % |
|---|---|---|---|
| **172** | Bn | 70 | 89 |
| **173** | *n*-Pr | 62 | 83 |

| Compound | R | Yield, % | ee, % |
|---|---|---|---|
| **174** | Bn | 85 | 84 |
| **175** | *n*-Pr | 74 | 83 |

**Scheme 6.9**. Synthesis of chiral piperidines by STAB reduction

# 7. Experimental Section

## 7.1. General information

Air- and/or moisture-sensitive reactions were carried out under an argon atmosphere in oven-dried glassware. Solvents and reagents were transferred by syringe or via cannula through rubber septa. Otherwise, the reactions were carried out in vessels open to the atmosphere.

**Reagents:** All reagents employed for the reactions which are commercially available (Aldrich, Alfa-Aesar, Fluka, Merck, Panreac, Probus, Scharlau) were used directly without further purification. When required, solvents were dried using standard procedures.

**Chromatography:** Analytical (TLC) thin layer chromatography was carried out using commercially available aluminium-backed plates coated with silica gel (Scharlau Cf 530 or Macherey-Nagel Alugram Sil G/UV254) or neutral aluminium oxide 60 F254 (UV254), with fluorescent indicator and

visualized under ultra-violet (UV) light lamp Camag UV-II (at 254 and 366 nm), staining with suitable stained solvents which prepared by standard reported procedure followed by heating or with molecular iodine.
Flash column chromatography was performed using silica gel SDS 60 ACC or Scharlau Ge 048 or neutral aluminium oxide Merck 90 standardized (0.063-0.200 mM, 70-230 mesh ASTM) and the eluent indicated in each case. Automated flash chromatography was performed in a Combiflash RF 200 system.

**Melting Point:** Melting points were determined by Stuart Scientific apparatus, SMP3 Model or a Kofler-type heating platine microscope from Reicher, 723 Model.

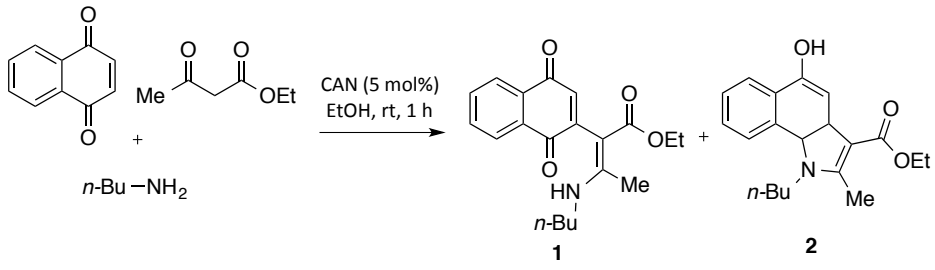
**IR Spectroscopy:** Infrared spectra (IR) were taken using a Perkin-Elmer FTIR Paragon 1000 spectrometer. Samples were prepared on sodium chloride window in a film form or as disks (potassium bromide).

**NMR Spectroscopy:** $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were recorded at 250 MHz spectrometer: Bruker AV-250 ($^{1}H$, 250 MHz; $^{13}C$, 63 MHz); $CDCl_3$ was used as solvent and chemical shifts are quoted in parts per million and reported as follows: chemical shift δ (ppm) (multiplicity, coupling constant *J* (Hz), number of protons, assignment). All the coupling constants are given in Hertz and multiplicity of $^{1}H$ signals indicated as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets) and td (triplet of doublets). Assignment of spectra was carried out using DEPT, COSY, NOESY, HMQC, and HMBC experiments.

**Elemental Analysis:** Quantitative combustion elemental analyses for carbon, hydrogen, nitrogen and sulfur were carried out by the CAI de Microanálisis from Universidad Complutense de Madrid, using a Leco CHNS 932 Elemental Analyzer.

## 7.2: A generalized, multicomponent version of the Nenitzescu indole synthesis: Synthesis of fused 5-hydroxy benzo[*g*]indole derivatives

### 7.2.1: General procedure for compounds 1 and 2




1 2

To a stirred mixture of primary amines (3 mmol) and 1,3-dicarbonyl compounds (3 mmol) in ethanol (6 mL) was added CAN (5 mol%) and stirred was continued for 30 min at room temperature. 1,4-naphthoquinone (3 mmol) was then added and the mixture was stirred for further 30 min at room temperature. After completion of the reaction, as indicated by tlc, dichloromethane (20 mL) was added to the mixture and the resulting solution was washed with water (5 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by silica column chromatography using petroleum ether-ethyl acetate mixture (gradient from 80:20-85-15, v/v) as eluent.

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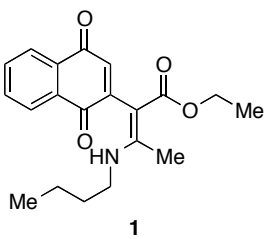
**(*E*)-Ethyl 3-(butylamino)-2-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)but-2-enoate (1):**




1

Prepared from ethyl acetoacetate (130 mg, 1 mmol), butyl amine (73 mg, 1 mmol), 1,4-napthoquinone (158 mg, 1 mmol), yield: 248 mg (73 %) as a brownish viscous liquid.

Data of **1**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 1.40–1.54 (m, 2H), 1.60–1.71 (m, 2H), 1.97 (s, 3H), 3.31 (q, *J* = 6.8 Hz, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 6.76 (s, 1H), 7.71–7.78 (m, 2H), 8.07–8.15 (m, 2H), 9.77 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.2, 14.7, 17.6, 20.5, 32.4, 43.8, 59.7, 89.7, 126.2, 127.2, 132.8, 133.3, 133.7, 133.8, 137.5, 149.4, 162.0, 169.2, 185.9, 186.0.

**IR** (NaCl): 2960, 2931, 1706, 1652, 1594 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{20}H_{23}NO_4$ (M = 341.16): C, 70.36; H, 6.79; N, 4.10. Found: C, 70.10; H, 6.41; N, 4.01 %.

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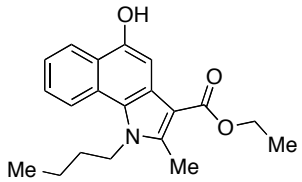
**Ethyl 1-butyl-5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3-carboxylate (2):**




**2**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), butyl amine (73 mg, 1 mmol), 1,4-napthoquinone (158 mg, 1 mmol), yield: 87 mg (27 %) as an off-white solid.

Data of **2**:

**$^{1}$H-NMR** (DMSO-$d_6$, 250 MHz): δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.37–1.48 (m, 5H), 1.73–1.84 (m, 2H), 2.77 (s, 3H), 4.28–4.36 (q, *J* = 7.1 Hz, 2H), 4.48–4.54 (t, *J* = 7.5 Hz, 2H), 7.43 (dd, *J* = 7.8, 7.1 Hz, 1H), 7.60 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.72 (s, 1H), 8.26–8.31 (m, 2H), 9.76 (s, 1H).

**$^{13}$C NMR** (DMSO-$d_6$, 63 MHz): δ 12.0, 14.0, 14.9, 19.7, 31.8, 40.8, 59.3, 102.0, 104.0, 120.6, 122.5, 122.8, 123.2, 123.6, 123.8, 124.8, 126.7, 143.0, 148.6, 165.6.

**IR** (KBr): 3266, 2963, 2933, 1646, 1599, 1521, 1415, 1334, 1247, 1123 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{20}H_{23}NO_3$ (M = 325.17): C, 73.82; H, 7.12; N, 4.30. Found: C, 73.53; H, 6.95; N, 4.19 %.

**MP**: 191-192 °C.

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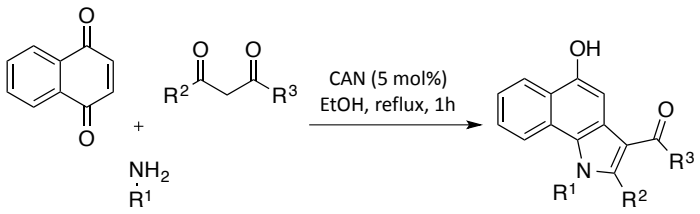
### 7.2.2: General procedure for the synthesis of compounds 2-14.




**2-14**

| Cmpd. | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **2** | *n*-Bu | Me | OEt |
| **3** | *n*-Bu | Me | OMe |
| **4** | $CH_2$-CH=$CH_2$ | Me | OEt |
| **5** | $CH_2$-Ph | Me | OEt |
| **6** | $CH_2$-CH=$CH_2$ | Me | OMe |
| **7** | $CH_2$-CH=$CH_2$ | Me | S-$^t$Bu |
| **8** | $CH_2$-C≡CH | Me | S-$^t$Bu |
| **9** | $CH_2$-C≡CH | Me | OEt |
| **10** | Ph | Me | OEt |
| **11** | *p*-$MeOC_6H_4$ | Me | OEt |
| **12** | *p*-$ClC_6H_4$ | Me | OEt |
| **13** | *n*-Bu | Me | S-$^t$Bu |
| **14** | *n*-Bu | *n*-Pr | OEt |

To a stirred mixture of the suitable primary amine (3 mmol) and 1,3-dicarbonyl compound (3 mmol) in ethanol (6 mL) was added CAN (5 mol%) and stirring was continued for 30 min at room temperature. 1,4-

naphthoquinone (3 mmol) was then added and the mixture was refluxed for further 30 min. After completion of the reaction, as indicated by TLC, dichloromethane (20 mL) was added to the mixture and the resulting solution was washed with water (5 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by silica column chromatography using petroleum ether-ethyl acetate mixture (gradient from 80:20-85-15, v/v) as eluent.

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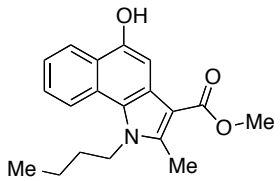
**Methyl 1-butyl-5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3-carboxylate (3):**




**3**

Prepared from methyl acetoacetate (130 mg, 1 mmol), butyl amine (73 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol), yield**:** 310 mg (96 %) as an off-white solid.

Data of **3**:

**$^1$H-NMR** (DMSO-$d_6$, 250 MHz): δ 0.95 (t, *J* = 7.2 Hz, 3H), 1.38–1.50 (m, 2H), 1.74–1.83 (m, 2H), 2.78 (s, 3H), 3.86 (s, 3H), 4.53 (t, *J* = 7.6 Hz, 2H), 7.44 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.62 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.69 (s, 1H), 8.27–8.34 (m, 2H), 9.79 (s, 1H).

**$^{13}$C NMR** (DMSO-$d_6$, 63 MHz): δ 12.1, 14.0, 19.7, 31.8, 45.4, 50.9, 101.9, 103.9, 120.6, 122.5, 122.9, 123.2, 123.4, 123.8, 124.7, 126.8, 143.1, 148.6, 166.0.

**IR** (NaCl): 3281, 2954, 1654, 1598, 1522, 1441, 1333, 1248, 1199 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{19}H_{21}NO_3$ (M = 311.15): C, 73.29; H, 6.80; N, 4.50. Found: C, 73.08; H, 6.67; N, 4.23 %.

**MP:** 221-222 °C.

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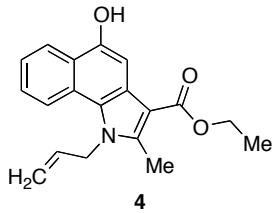
**Ethyl 1-allyl-5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3-carboxylate(4):**




**4**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), allyl amine (57 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol), yield: 278 mg (90 %) as an off-white solid.

Data of **4**:

**$^{1}$H-NMR** (DMSO-$d_6$, 250 MHz): δ *d* 1.41 (t, *J* = 7 Hz, 3H), 2.73 (s, 3H), 4.33 (q, *J* = 7.0 Hz, 2H), 4.65 (d, *J* = 17.2 Hz, 1H), 5.17–5.22 (m, 3H), 6.21–6.38 (m, 1H), 7.42 (dd, *J* = 7.8, 7.1 Hz, 1H), 7.54 (dd, *J* = 7.7, 6.8 Hz, 1H), 7.72 (s, 1H), 8.21–8.28 (m, 2H), 9.79 (s, 1H).

**$^{13}$C NMR** (DMSO-$d_6$, 63 MHz): δ 11.7, 14.9, 48.0, 59.4, 101.9, 104.3, 116.0, 120.9, 122.3, 122.9, 123.3, 123.6, 123.8, 124.4, 126.4, 133.9, 143.3, 148.6, 165.6.

**IR** (KBr): 3259, 2981, 1644, 1597, 1529, 1418, 1336, 1245, 1131 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{19}H_{19}NO_3$ (M = 309.14): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.48; H, 6.16; N, 4.54 %.

**MP:** 218-219 °C.

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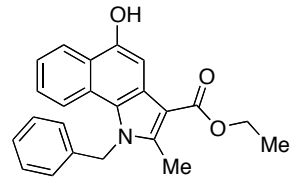
**Ethyl 1-benzyl-5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3-carboxylate (5):**




**5**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), benzyl amine (107 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol), yield: 323 mg (90 %) as an off-white solid.

Data of **5**:

**$^{1}$H-NMR** (DMSO-$d_6$, 250 MHz): δ 1.43 (t, *J* = 7.0 Hz, 3H), 2.74 (s, 3H), 4.35 (q, *J* = 7.0 Hz, 2H), 5.90 (s, 2H), 7.05 (d, *J* = 7.4 Hz, 2H), 7.25–7.37 (m, 5H), 7.76 (s, 1H), 8.07–8.10 (m, 1H), 8.22–8.25 (m, 1H), 9.83 (s, 1H).

**$^{13}$C NMR** (DMSO-$d_6$, 63 MHz): δ 11.9, 14.9, 49.1, 59.5, 101.9, 104.6, 120.7, 122.3, 122.9, 123.4, 123.6, 123.8, 124.7, 125.9, 126.4, 127.6, 129.3, 137.4, 143.6, 148.8, 165.6.

**IR** (KBr): 3264, 2928, 1641, 1599, 1523, 1416, 1336, 1293, 1247, 1124 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{23}H_{21}NO_3$ (M = 359.15): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.50; H 6.05; N, 3.78 %.

**MP:** 240-241 °C.

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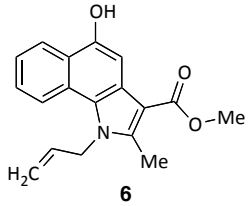
**Methyl 1-allyl-5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3-carboxylate (6):**



**6**

Prepared from methyl acetoacetate (116 mg, 1 mmol), ally amine (57 mg, 1 mmol), 1,4-naphthoquinone (158 mg, 1 mmol), yield: 262 mg (89 %) as an off-white solid.

Data of **6**:

**$^{1}$H-NMR** (DMSO-$d_6$, 250 MHz): δ 2.74 (s, 3H), 3.88 (s, 3H), 4.36 (d, *J* = 17.2 Hz, 1H), 5.19–5.24 (m, 3H), 6.25–6.36 (m, 1H), 7.44 (dd, *J* = 7.6, 7.1 Hz, 1H), 7.56 (dd, *J* = 7.5, 6.9 Hz, 1H), 7.71 (s, 1H), 8.23–8.30 (m, 2H), 9.81 (s, 1H).

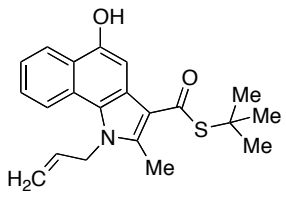
**$^{13}$C NMR** (DMSO-$d_6$, 63 MHz): δ 11.7, 48.1, 50.9, 101.8, 104.1, 116.0, 120.9, 122.3, 123.0, 123.4, 123.6, 123.8, 124.3, 126.5, 133.9, 143.4, 148.7, 165.9.

**IR** (KBr): 3256, 2980, 1644, 1623, 1597, 1530, 1415, 1335, 1245, 1130, 1071 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{18}H_{17}NO_3$ (M = 295.12): C, 73.20; H, 5.80; N, 4.74. Found: C, 72.96; H, 6.17; N, 4.52 %.

**MP:** 220-221 °C**.**

***S-tert*-Butyl 1-allyl-5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3-carbothioate (7):**




**7**

Prepared from *S-tert*-butyl 3-oxobutanethioate (174 mg, 1 mmol), allyl amine (57 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol), yield: 307 mg (87 %) as a pale brown solid.

Data of **7**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ (Hydroxyl proton merged) 1.68 (s, 9H), 2.72 (s, 3H), 4.90 (d, *J* = 17.5 Hz, 1H), 5.02 (s, 2H), 5.29 (d, *J* = 12.5 Hz, 1H), 6.13–6.25 (m, 1H), 7.43–7.55 (m, 2H), 7.90 (s, 1H), 8.13 (d, *J* =8.0 Hz, 1H), 8.36 (d, *J* = 7.0 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63MHz): δ 12.9, 30.9, 48.5, 48.9, 103.2, 115.9, 117.9, 120.9, 122.5, 122.9, 123.4, 123.6, 123.7, 125.4, 126.6, 132.4, 141.0, 147.4, 189.3.

**IR** (KBr): 3377, 2963, 1622, 1597, 1512, 1401, 1363, 1265, 1091 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{21}H_{23}NSO_2$ (M = 353.14): %C, 71.36, %H, 6.56, %N, 3.96, %S, 9.07; Found: %C, 71.08, %H, 6.36, %N, 4.16, %S, 8.73

**MP:** 107-108 °C.

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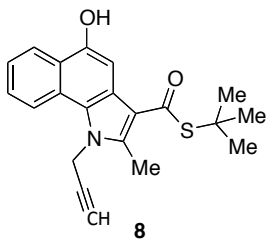
***S-tert*-butyl 5-hydroxy-2-methyl-1-(prop-2-yn-1-yl)-1*H*-benzo[*g*]indole-3-carbothioate (8):**




**8**

Prepared from *S-tert*-butyl 3-oxobutanethioate (174 mg, 1 mmol), propargyl amine (55 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol), yield: 308 mg (88 %) as a pale brown solid.

Data of **8**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz): δ 1.66 (s, 9H), 2.20(s, 1H), 2.86 (s, 3H), 5.16 (s, 2H), 7.28 (s, 1H), 7.51–7.64(m, 2H), 7.83 (s, 1H), 8.38 (d, *J* = 7.5 Hz, 1H), 8.47 (d, *J* = 7.5 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63MHz): δ 13.1, 30.8, 36.6, 48.9, 74.8, 76.6, 103.0, 116.3, 121.0, 122.5, 122.8, 123.4, 123.7, 123.8, 125.1, 126.9, 140.0, 147.6, 189.3.

**IR** (KBr): 3296, 2964, 2923, 1668, 1652, 1512, 1455, 1364, 1264, 1083 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{21}H_{21}NSO_2$ (M = 351.13): C, 71.76; H, 6.02; N, 3.99; S, 9.12. Found: C, 71.48; H, 5.72; N, 4.17; S, 8.92 %.

**MP:** 168-169 °C.

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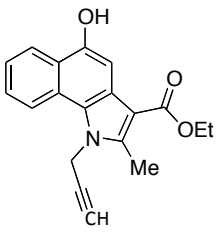
**Ethyl 5-hydroxy-2-methyl-1-(prop-2-yn-1-yl)-1*H*-benzo[*g*]indole-3-carboxylate (9):**




**9**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), propargyl amine (55 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol), yield: 230 mg (75 %) as an off-white solid.

Data of **9**:

**$^{1}$H-NMR** (DMSO-$d_6$, 250 MHz): δ 1.41 (t, *J* = 7.0 Hz, 3H), 2.81 (s, 3H), 3.53 (s, 1H), 4.33 (q, *J* = 7.0 Hz, 2H), 5.40 (s, 2H), 7.46 (dd, *J* = 7.8, 7.7 Hz, 1H), 7.62 (dd, *J* = 7.9, 7.8 Hz, 1H), 7.70 (s, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 8.50 (d, *J* = 8.6Hz, 1H), 9.84 (s, 1H).

**$^{13}$C NMR** (DMSO-$d_6$, 63 MHz): δ 11.9, 14.8, 36.3, 59.5, 76.8, 79.2, 101.8, 104.7, 121.2, 122.4, 123.2, 123.4, 123.5, 123.6, 124.4, 126.5, 142.8, 148.8, 165.4.

**IR** (KBr): 3305, 2976, 2924, 1635, 1598, 1525, 1457, 1418, 1336, 1244, 1133 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{19}H_{17}NO_3$ (M = 307.12): C, 74.25; H, 5.58; N, 4.56. Found: C, 74.01; H, 5.70; N, 4.34 %.

**MP:** 235-236 °C.

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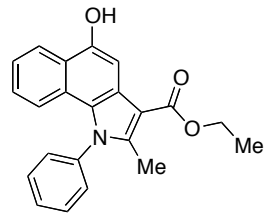
**Ethyl 5-hydroxy-2-methyl-1-phenyl-1*H*-benzo[*g*]indole-3-carboxylate (10):**




**10**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), aniline (93 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol), yield: 224 mg (65 %), pale brown solid.

Data of **10**:

**$^{1}$H-NMR** (DMSO-$d_6$, 250 MHz): δ 1.42 (t, *J* = 7.0 Hz, 3H), 2.43 (s, 3H), 4.36 (q, *J* = 7.0 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 1H), 7.13 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.51–7.54 (m, 2H), 7.72–7.75 (m, 4H), 8.22 (d, *J* = 8.3 Hz, 1H), 9.87 (s, 1H).

**$^{13}$C NMR** (DMSO-$d_6$, 63 MHz): δ 13.0, 15.0, 59.5, 101.7, 105.1, 119.9, 122.3, 123.1, 123.4, 123.7, 124.2, 124.8, 125.9, 129.2, 130.2, 130.8, 139.3, 143.5, 148.9, 165.6.

**IR** (KBr): 3420, 2931, 1648, 1596, 1496, 1411, 1337, 1246, 1196, 1177, 1071 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{22}H_{19}NO_3$ (M = 345.14): C, 76.50; H, 5.54; N, 4.06. Found: C, 76.47; H, 5.56; N, 4.15 %.

**MP:** 230-231 °C.

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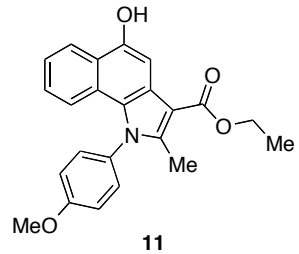
**Ethyl 5-hydroxy-1-(4-methoxyphenyl)-2-methyl-1*H*-benzo[*g*]-indole-3-carboxylate (11):**




**11**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), 4-methoxyaniline (123 mg, 1 mmol) and

1,4-naphthoquinone (158 mg, 1 mmol), yield: 273 mg (73 %) as a pale brown solid.

Data of **11**:

**$^{1}$H-NMR** (DMSO-$d_6$, 250 MHz): δ 1.41 (t, *J* = 7.0 Hz, 3H), 2.43 (s, 3H), 3.93 (s, 3H), 4.35 (q, *J* = 7.0 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.15–7.46 (m, 6H), 7.74 (s, 1H), 8.22 (d, *J* = 8.3 Hz, 1H), 9.84 (s, 1H).

**$^{13}$C NMR** (DMSO-$d_6$, 63 MHz): δ 13.0, 14.9, 55.9, 59.4, 101.7, 104.9, 115.8, 119.9, 122.4, 123.0, 123.4, 123.6, 124.0, 125.0, 125.9, 130.2, 131.7, 143.9, 148.9, 160.1, 165.6.

**IR** (KBr): 3273, 2928, 1652, 1514, 1384, 1298, 1249, 1176, 1136, 1033 $cm^{-1}$;

**Elemental analysis:** Anal. Calcd for $C_{23}H_{21}NO_4$ (M = 375.15): C, 73.58; H, 5.64; N, 3.73. Found: C, 73.28; H, 5.77; N, 3.85 %.

**MP:** 216-217 °C.

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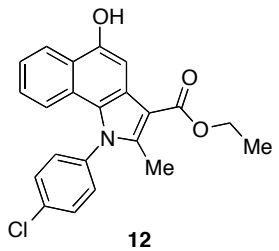
**Ethyl 1-(4-chlorophenyl)-5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3-carboxylate (12):**




**12**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), 4-choloraniline (127 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol), yield: 288 mg (76 %) as an off-white solid.

Data of **12**:

**$^{1}$H-NMR** (DMSO-$d_6$, 250 MHz): δ 1.41 (t, *J* = 7.0 Hz, 3H), 2.42 (s, 3H), 4.36 (q, *J* = 7.0 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 1H), 7.21 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.33 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.57–7.61 (m, 2H), 7.74–7.81 (m, 3H), 8.23 (d, *J* = 8.2 Hz, 1H), 9.90 (s, 1H).

**$^{13}$C NMR** (DMSO-$d_6$, 63 MHz): δ 13.0, 14.8, 59.5, 101.6, 105.4, 119.7, 122.2, 123.2, 123.5, 123.8, 124.3, 124.9, 126.2, 130.8, 131.1, 134.9, 138.4, 143.5, 149.2, 165.3.

**IR** (KBr): 3282, 2927, 1649, 1493, 1386, 1339, 1259, 1137, 1090, 1015 $cm^{-1}$;

**Elemental analysis:** Anal. Calcd for $C_{22}H_{18}ClNO_3$ (M = 379.10): C, 69.57; H, 4.78; N, 3.69. Found: C, 69.27; H, 4.94; N, 3.84 %.

**MP:** 250-251 °C.

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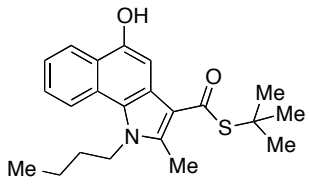
***S*-*tert*-Butyl 1-butyl-5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3-carbothioate (13):**




**13**

Prepared from *S*-*tert*-butyl 3-oxobutanethioate (174 mg, 1 mmol), butyl amine (73 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol)**,** yield: 258 mg (70 %) as a dark brown viscous liquid.

Data of **13**:

**$^{1}$H-NMR** ($CDCl_3$, 250MHz): δ 1.04 (t, *J* = 7.2 Hz, 3H), 1.52–1.61 (m, 2H), 1.67 (s, 9H), 1.89–1.95 (m, 2H), 2.80 (s, 3H), 4.43 (t, *J* = 7.3 Hz, 2H), 5.43 (s, 1H), 7.48–7.62 (m, 2H), 7.90 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.39 (d, 8.2 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63MHz): δ (one aromatic carbon signal is merged with others) 13.3, 14.2, 20.5, 30.9, 32.2, 46.0, 48.9, 103.2, 115.8, 120.6, 122.9, 123.7, 123.4, 123.9, 124.8, 126.8, 140.5, 147.3, 189.4.

**IR** (NaCl): 2968, 2871, 1668, 1597, 1504, 1456, 1364, 1248, 1166 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{22}H_{27}NO_2S$ (M = 369.18): C, 71.51; H, 7.36; N, 3.79; S, 8.68**.** Found: C, 71.25; H, 7.15; N, 3.58; S, 8.46 %.

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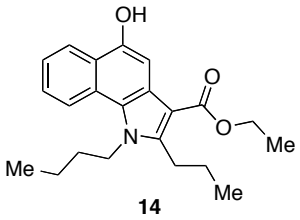
**Ethyl 1-butyl-5-hydroxy-2-propyl-1*H*-benzo[*g*]indole-3-carboxylate (14):**



**14**

Prepared from ethyl 3-oxohexanoate (158 mg, 1 mmol), butyl amine (73 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol), yield: 183 mg (52 %), as an off-white solid.

Data of **14**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz): δ 1.03–1.14 (m, 6H), 1.48–1.58 (m, 5H), 1.67–1.77 (m, 2H), 1.91–1.98 (m, 2H), 3.22 (t, *J* = 7.5 Hz, 2H), 4.46–4.55 (m, 4H), 6.59 (br-s, 1H), 7.46–7.64 (m, 2H), 8.02 (s, 1H), 8.25 (dd, *J* = 8.5 Hz, 1H), 8.46 (d, *J* = 8.3 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.2, 14.7, 14.9, 20.5, 24.0, 28.3, 32.8, 46.0, 60.2, 102.9, 104.5, 120.5, 123.0, 123.2, 123.6, 124.1, 124.6, 125.5, 126.7, 147.3, 148.0, 166.9.

**IR** (KBr): 2959, 2870, 1654, 1600, 1513, 1450, 1332, 1245, 1124, 1070 $cm^{-1}$;

**Elemental analysis:** Anal. Calcd for $C_{22}H_{27}NO_3$ (M = 353.20): C, 74.76; H, 7.70; N, 3.96. Found: C, 74.37; H, 7.43; N, 4.29 %.

**MP:** 166-167 °C.

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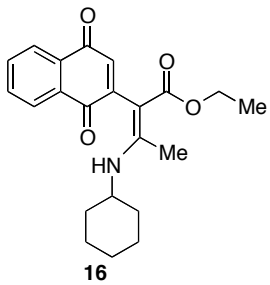
**7.2.3: (*E*)-Ethyl 3-(cyclohexylamino)-2-(1,4-dioxo-1,4-dihydronaphthalen-2-yl) but-2-enoate (16):**



**16**

To a stirred mixture of ethyl acetoacetate (130 mg, 1 mmol) and cyclohexanamine (99 mg, 1 mmol) in ethanol (6 mL) was added CAN (5 mol%) and stirring was continued for 30 min at reflux. 1,4-naphthoquinone (158 mg, 1 mmol) was then added and the mixture was stirred for further 30 min at reflux. After completion of the reaction, as monitored on TLC,

dichloromethane (20 mL) was added to the mixture and the resulting solution was washed with water (5 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by silica column chromatography using petroleum ether-ethyl acetate mixture (85:15, v/v) as eluent to give **16** as a pale brown viscous oil.

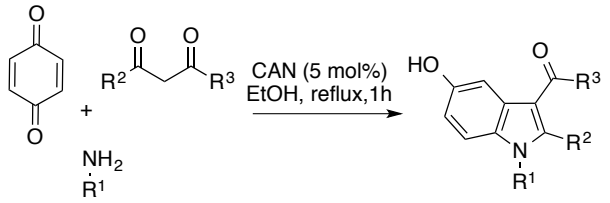
Data of **16**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.14 (t, *J* = 7.0 Hz, 3H), 1.28-1.43 (m, 6H), 1.80-1.83 (m, 2H), 1.85-2.21 (m, 5H), 3.44 (m, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 6.79 (s, 1H), 7.73-7.76 (m, 2H), 8.10-8.12 (m, 2H), 9.88 (d, *J* = 7.9 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.7, 17.3, 15.0, 15.7, 34.4, 52.5, 59.6, 89.9, 126.2, 127.2, 132.8, 133.3, 133.7, 133.8, 137.5, 149.5, 160.8, 169.2, 185.9, 186.0.

**IR** (NaCl): 2932, 2855, 1667, 1644, 1593, 1463, 1147, 1102, 1069 $cm^{-1}$.

### 7.2.4: General procedure for the synthesis of 5-hydroxyindole derivatives 17-24.

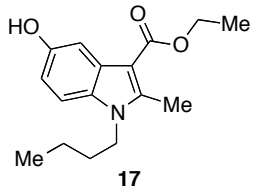



**17-24**

| Compd | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **17** | *n*-Bu | Me | OEt |
| **18** | $CH_2$-CH=$CH_2$ | Me | OEt |
| **19** | $CH_2$-Ph | Me | OEt |
| **20** | $CH_2$-C≡CH | Me | OEt |
| **21** | *n*-Bu | Me | S-$^t$Bu |
| **22** | $CH_2$-CH=$CH_2$ | Me | S-$^t$Bu |
| **23** | *n*-Bu | *n*-Pr | OEt |
| **24** | $CH_2$-CH=$CH_2$ | *n*-Pr | OEt |

To a stirred mixture of primary amines (1 mmol) and 1,3-dicarbonyl compounds (1 mmol) in ethanol (3 mL) was added CAN (5 mol%) and stirred was continued for 30 min at room temperature. *p*-benzoquinone (1 mmol) was then added and the mixture was refluxed for further 30 min. After completion of the reaction, as indicated by TLC, dichloromethane (20 mL) was added to the mixture and the resulting solution was washed with water (5 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by silica column chromatography using petroleum ether-ethyl acetate mixture (gradient from 85:15-88:12, v/v) as eluent.

**Ethyl 1-butyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (17):**




**17**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), butyl amine (73 mg, 1 mmol) and *p*-benzoquinone (108 mg, 1 mmol), yield: 214 mg (78 %) as an off-white solid.

Data of **17**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz): δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.33–1.49 (m, 5H), 1.75 (m, 2H), 2.76 (s, 3H), 4.09 (t, *J* = 7.4 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.98 (s, 1H), 6.81 (dd, *J* = 2.3, 8.7 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 12.6, 14.2, 14.9, 20.6, 32.3, 43.6, 60.0, 103.6, 106.7, 110.4, 111.7, 128.3, 131.3, 145.5, 152.1, 167.0.

**IR** (KBr): 2965, 2927, 2863, 1652, 1621, 1520, 1469, 1440, 1379, 1283, 1245, 1185, 1157, 1116 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{16}H_{21}NO_3$ (M = 275.15): C, 69.79; H, 7.69; N, 5.09. Found: C, 69.51; H, 7.52; N, 5.30 %.

**MP:** 145-146 °C.

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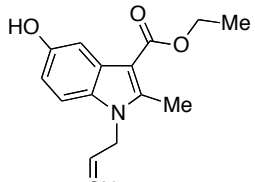
**Ethyl 1-allyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (18):**




**18**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), allyl amine (57 mg, 1 mmol) and *p*-benzoquinone (108 mg, 1 mmol) as a yield: 194 mg (75 %) as a pale brown solid.

Data of **18**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz): δ 1.35 (t, *J* = 7.1 Hz, 3H), 2.62 (s, 3H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.58–4.61 (m, 2H), 4.74 (dq, *J* = 0.85, 17.1 Hz, 1H), 5.07 (dq, *J* =

0.85, 10.3 Hz, 1H), 5.75–5.92 (m, 2H), 6.72 (dd, *J* = 2.5, 8.7 Hz, 1H), 7.02 (d, *J* = 8.7, 1H), 7.62 (d, *J* = 2.4 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 12.3, 15.0, 45.8, 60.0, 104.0, 106.8, 110.5, 111.9, 117.2, 128.2, 131.4, 132.3, 145.7, 152.1, 166.9.

**IR** (KBr): 3288, 2986, 1655, 1620, 1522, 1471, 1433, 1379, 1292, 1249, 1185, 1155, 1120, 1034 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{15}H_{17}NO_3$ (M = 259.12): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.20; H, 6.63; N, 5.49 %.

**MP:** 132-133 °C.

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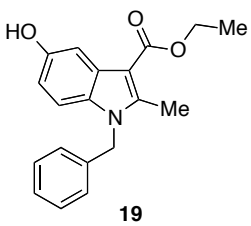
**Ethyl 1-benzyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (19):**




**19**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), benzyl amine (107 mg, 1 mmol) and *p*-benzoquinone (108 mg, 1 mmol), yield: 225 mg (73 %) as an off-white solid.

Data of **19**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz): δ 1.48 (t, *J* = 7.1 Hz, 3H), 2.74 (s, 3H), 4.42 (q, *J* = 7.1 Hz, 2H), 5.34 (s, 2H), 6.78 (dd, *J* = 2.5, 8.7 Hz, 1H), 7.00 (dd, *J* = 2.4, 7.8 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 7.29–7.35 (m, 5H), 7.66 (d, *J* = 2.5 Hz, 1H);

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 12.5, 15.0, 47.0, 60.0, 104.4, 106.9, 110.7, 111.9, 126.3, 128.0, 128.2, 129.4, 131.9, 136.7, 146.0, 151.9, 166.7.

**IR** (KBr): 3291, 2971, 2926, 1644, 1623, 1520, 1475, 1438, 1358, 1293, 1249, 1180, 1142, 1120, 1032 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{19}H_{19}NO_3$ (M = 309.14): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.42; H, 6.37; N, 4.47 %.

**MP:** 191-192 °C.

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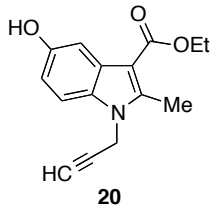
**Ethyl 5-hydroxy-2-methyl-1-(prop-2-yn-1-yl)-1*H*-indole-3-carboxylate (20):**



**20**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), propargyl amine (55 mg, 1 mmol) and *p*-benzoquinone (108 mg, 1 mmol), yield: 177 mg (69 %) as an off-white solid.

**$^{1}$H-NMR** (DMSO-$d_6$, 250 MHz): δ 1.41 (t, *J* = 6.9 Hz, 3H), 2.14 (s, 1H), 2.78 (s, 3H), 3.42 (s, 2H), 5.15 (q, *J* = 7 Hz, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 7.44 (s, 2H), 9.08 (s, 1H).

**$^{13}$C NMR** (DMSO-$d_6$, 63 MHz) δ: 12.4, 15.3, 33.1, 59.7, 75.9, 79.5, 103.8, 106.4, 111.4, 112.5, 127.9, 130.5, 145.4, 153.7, 165.9.

**IR** (KBr): 3285, 2985, 1654, 1622, 1528, 1486, 1434, 1378, 1348, 1292, 1249, 1184, 1151, 1126, 1034 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{15}H_{15}NO_3$ (M = 257.11): C, 70.20; H, 5.88; N, 5.44**.** Found: C, 69.90; H, 5.55; N, 5.20 %.

**MP:** 201-202 °C.

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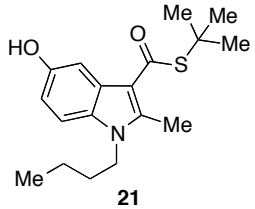
***S-tert*-butyl 1-butyl-5-hydroxy-2-methyl-1*H*-indole-3-carbothioate (21):**



**21**

Prepared from S-tert-butyl 3-oxobutanethioate (174 mg, 1 mmol), butyl amine (73 mg, 1 mmol) and *p*-benzoquinone (108 mg, 1 mmol), yield: 274 mg (86 %) as an off-white solid.

Data of **21**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz): δ 0.97 (t, *J* = 7.1 Hz, 3H), 1.32–1.47 (m, 2H), 1.64 (s, 9H), 1.69–1.74 (m, 2H), 2.74 (s, 3H), 4.06 (t, *J* = 7.4 Hz, 2H), 5.05 (s, 1H), 6.83 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.80 (d, *J* = 2.1 Hz, 1H);

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 13.4, 14.2, 20.6, 30.9, 32.2, 43.5, 48.5, 107.4, 110.6, 111.6, 114.0, 126.5, 131.4, 143.7, 151.7, 188.6.

**IR** (KBr): 3438, 2959, 2870, 1627, 1596, 1587, 1495, 1459, 1412, 1362, 1321, 1197, 1163, 1067 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{18}H_{25}NO_2S$ (M = 319.16): C, 67.67; H, 7.89; N, 4,38; S, 10.04. Found: C, 67.48; H, 7.72; N, 4,65; S, 9.90 %.

**MP:** 133-134 °C.

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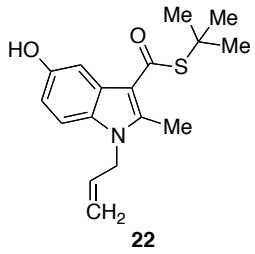
***S*-*tert*-butyl 1-allyl-5-hydroxy-2-methyl-1*H*-indole-3-carbothioate (22):**




**22**

Prepared from *S*-*tert*-butyl 3-oxobutanethioate (174 mg, 1 mmol), allyl amine (57 mg, 1 mmol) and *p*-benzoquinone (108 mg, 1 mmol), yield: 245 mg (81 %) as a pale brownish viscous liquid.

Data of **22**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz): δ 1.64 (s, 9H), 2.70 (s, 3H), 4.65–4.67 (m, 2H), 4.84 (d, *J* = 17.1 Hz, 1H), 5.16 (d, *J* = 10.3 Hz, 1H), 5.57 (s, 1H), 5.82–5.97 (m, 1H), 6.82 (dd, *J* = 2.3, 8.7 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 7.82 (d, *J* = 2.3 Hz. 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 13.1, 30.8, 45.6, 48.6, 107.4, 110.6, 111.9, 114.3, 117.3, 126.5, 131.4, 132.1, 143.9, 152.0, 188.9.

**IR** (NaCl): 2962, 2922, 1622, 1597, 1501, 1473, 1409, 1362, 1219, 1164, 1085, 1065, 1021 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{17}H_{21}NO_2S$ (M = 303.13): C, 67.29; H, 6.98; N, 4.62; S, 10.57. Found: C, 67.03; H, 6.96; N, 4.63; S, 10.36 %.

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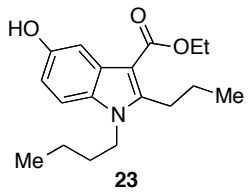
**Ethyl 1-butyl-5-hydroxy-2-propyl-1*H*-indole-3-carboxylate (23):**



**23**

Prepared from ethyl 3-oxohexanoate (158 mg, 1 mmol), butyl amine (73 mg, 1 mmol) and *p*-benzoquinone (108 mg, 1 mmol), yield: 248 mg (82 %) as an off-white solid.

Data of **23**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 7.5 Hz, 3H), 1.07 (t, *J* = 7.3 Hz, 3H), 1.35–1.50 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H), 1.65–1.83 (m, 4H), 3.09–3.15 (m, 2H), 4.08 (t, *J* = 7.3 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 5.79 (s, 1H), 6.84 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.2, 14.7, 14.9, 20.7, 23.7, 28.4, 32.6, 43.7, 60.0, 103.0, 106.8, 110.7, 111.8, 128.5, 131.2, 149.7, 152.3, 166.8.

**IR** (KBr): 3336, 2961, 2872, 1688, 1651, 1521, 1470, 1444, 1379, 1296, 1245, 1180, 1147, 1111, 1035 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{18}H_{25}NO_3$ (M = 303.18): C, 71.26; H, 8.31; N, 4.62. Found: C, 71.00; H, 8.11; N, 4.66 %.

**MP**: 124-125 °C.

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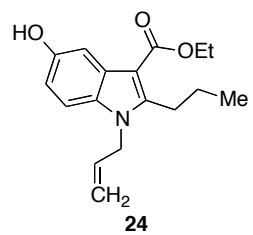
**Ethyl 1-allyl-5-hydroxy-2-propyl-1*H*-indole-3-carboxylate (24):**



**24**

Prepared from ethyl 3-oxohexanoate (158 mg, 1 mmol), allyl amine (57 mg, 1 mmol) and *p*-benzoquinone (108 mg, 1 mmol), yield: 223 mg (78 %), pale brown solid.

Data of **24**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz): δ 1.06 (t, *J* = 7.2 Hz, 3H), 1.46 (t, *J* = 7.0 Hz, 3H), 1.62–1.72 (m, 2H), 3.10 (t, *J* = 7.6 Hz, 2H), 4.41 (q, *J* = 7.0 Hz, 2H), 4.73 (s, 2H), 4.88 (d, *J* = 17.4 Hz, 1H), 5.19 (d, *J* = 10.0 Hz, 1H), 5.65 (s, 1H), 5.89–

6.00 (m, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.72 (s, 1H);

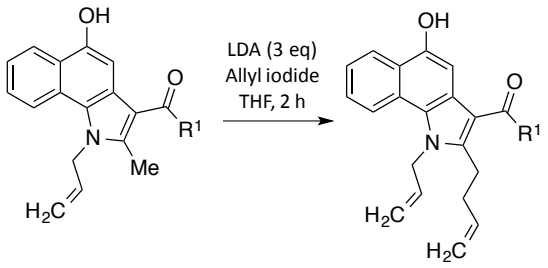
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 14.9, 23.5, 28.2, 45.9, 60.0, 103.6, 106.8, 110.9, 111.9, 117.3, 128.4, 131.4, 132.8, 149.9, 152.3, 166.6;

**IR** (KBr): 3362, 2964, 2870, 1691, 1659, 1525, 1470, 1378, 1247, 1182, 1148, 1115 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{17}H_{21}NO_3$ (M = 287.15): C, 71.06; H, 7.37; N, 4.87. Found: C, 70.86; H, 7.13; N, 5.11 %.

**MP:** 116-117 °C.

### 7.2.5: General procedure for the introduction of allyl substituents on the C-2 methyl group of 4 and 6: Synthesis of compounds 25 and 26.




**25-26**

A solution of compounds **4** or **6** (1 mmol) in dry THF (4 mL) was added to LDA (3 mmol), prepared from BuLi (3.3 mmol) and diisopropylamine (3 mmol) in dry THF (4 mL), slowly at -20 °C and the reaction mixture was stirred for 30 min at the same temperature. Allyl iodide (2.2 mmol) was then added and stirring was continued for further 2 h. The reaction was quenched by adding saturated $NH_4Cl$ solution and extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$ and the solvent was evaporated. The crude mixture was purified by silica column chromatography eluting with petroleum ether-ethyl acetate mixture (80 : 20, v/v).

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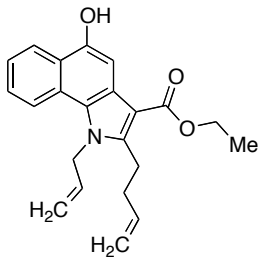
**Ethyl 1-allyl-2-(but-3-enyl)-5-hydroxy-1*H*-benzo[*g*]indole-3-carboxylate (25):**




**25**

Prepared from compound **4** (311 mg, 1 mmol), allyl iodide (367 mg, 2.2 mmol), yield: 279 mg (80 %) as an off-white solid.

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.50 (t, *J* = 7.1 Hz, 3H), 2.46 (q, *J* = 6.7 Hz, 2H), 3.29 (t, *J* = 6.8 Hz, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.90 (d, *J* = 17.1 Hz, 1H), 5.09 (d, *J* = 14.2 Hz, 2H), 5.20 (s, 3H), 5.32 (d, *J* = 9.4 Hz, 1H), 5.89–6.05 (m, 1H),

6.21–6.32 (m, 1H), 7.46-7.60 (m, 2H), 7.96 (s, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.42 (d, *J* = 8.2 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 15.0, 25.7, 34.4, 48.3, 60.2, 102.8, 105.1, 115.8, 117.9, 120.9, 122.7, 123.5, 123.6, 123.9, 124.9, 125.2, 126.6, 133.0, 137.8, 146.7, 147.9, 166.6.

**IR** (KBr): 3288, 2984, 1635, 1622, 1599, 1512, 1450, 1128, 1072, 987 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{22}H_{23}NO_3$ (M = 349.17): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.36; H, 6.53; N, 3.74 %.

**MP**: 181–182 °C.

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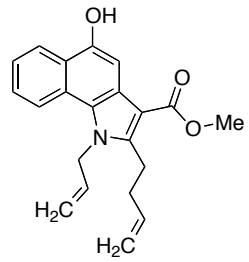
**Methyl 1-allyl-2-(but-3-enyl)-5-hydroxy-1*H*-benzo[*g*]indole-3-carboxylate (26).**



**26**

Prepared from compound **6** (297 mg, 1 mmol), allyl iodide (367 mg, 2.2 mmol), yield: 257 mg (77 %) as an off-white solid.

Data of **26**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 2.46 (q, *J* = 6.7 Hz, 2H), 3.28 (t, *J* = 5.4 Hz, 2H), 4.03 (s, 3H), 4.90 (d, *J* = 17.1 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 5.19 (s, 3H), 5.33 (d, *J* = 10.5 Hz, 1H), 5.89–6.05 (m, 1H), 6.19–6.33 (m, 1H), 6.58 (s, 1H), 7.47–7.60 (m, 2H), 8.02 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.45 (d, *J* = 8.2 Hz, 1H).

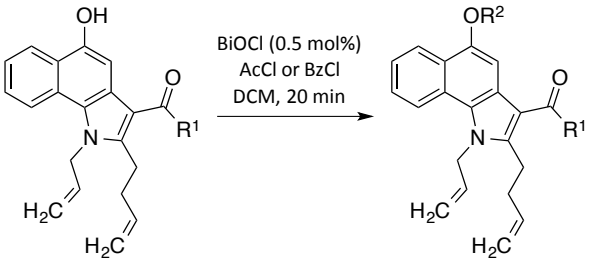
**$^{13}$CNMR** ($CDCl_3$, 63MHz): δ 25.7, 34.4, 48.3, 51.5, 102.8, 104.9, 115.9, 117.9, 121.0, 122.8, 123.4, 123.6, 123.9, 124.9, 125.2, 126.6, 133.0, 137.8, 146.9, 148.1, 167.0.

**IR** (KBr): 3311, 2985, 1638, 1598, 1450, 1334, 1243, 1126 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{21}H_{21}NO_3$ (M = 335.15): C, 75.20; H, 6.31; N, 4.18. Found: C, 74.84; H, 6.28; N, 4.02 %.

**MP**: 181–182 °C.

### 7.2.6: General procedure for the synthesis of compounds 27-30.




**27-30**

To a stirred suspension of compound **25-26** (1 mmol) and BiOCl (5–10 mol%) in dichloromethane (3 mL) under argon was added acetyl or benzoyl chloride (2 mmol) at room temperature. The reaction was completed in 20 min as indicated by TLC. The mixture was diluted with dichloromethane (10 mL), washed with saturated $NaHCO_3$ solution, water and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and the solvent was evaporated. Purification of the crude mixture by $Al_2O_3$ (neutral, activity grade II-III) column chromatography eluting with petroleum ether–ethyl acetate mixture (85 : 15, v/v) gave the compounds **27-30**.

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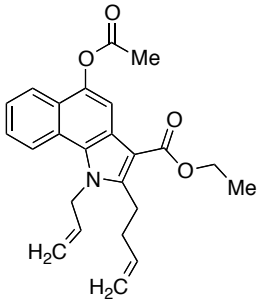
**Ethyl 5-acetoxy-1-allyl-2-(but-3-enyl)-1*H*-benzo[*g*]indole-3-carboxylate (27).**




**27**

Prepared from compound **25** (351 mg, 1 mmol), acetyl chloride (156 mg, 2 mmol), yield: 371 mg (95 %) as an off-white solid.

Data of **27**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.49 (t, *J* = 7.1 Hz, 3H), 2.41–2.53 (m, 5H), 3.31 (t, *J* = 7.6 Hz, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.91 (d, *J* = 17.1 Hz, 1H), 5.05 (d, *J* = 10.8

Hz, 1H), 5.19 (d, *J* = 10.6 Hz, 3H), 5.33 (d, *J* = 10.5 Hz, 1H), 5.88–6.04 (m, 1H), 6.22–6.33 (m, 1H), 7.47–7.60 (m, 2H), 7.96 (d, *J* = 7.9 Hz, 1H), 8.18 (s, 1H), 8.27 (d, *J* = 8.7 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 15.0, 21.5, 25.5, 34.3, 48.3, 60.1, 106.3, 113.7, 115.9, 118.2, 121.6, 122.6, 122.9, 123.8, 124.5, 125.0, 126.6, 128.2, 132.8, 137.7, 142.6, 147.7, 165.8, 170.6.

**IR** (KBr): 2982, 1761, 1693, 1527, 1418, 1365, 1206, 1149 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{24}H_{25}NO_4$ (M = 391.18): C, 73.64; H, 6.44; N, 3.58. Found: C, 73.39; H, 6.40; N, 3.71 %.

**Mp**: 101–102 °C.

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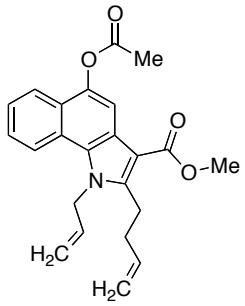
**Methyl 5-acetoxy-1-allyl-2-(but-3-enyl)-1*H*-benzo[*g*]indole-3-carboxylate (28).**



**28**

Prepared from compound **26** (337 mg, 1 mmol), acetyl chloride (156 mg, 2 mmol), yield: 354 mg (94 %) as an off-white solid.

Data of **28**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 2.41–2.53 (m, 5H), 3.32 (t, *J* = 7.7 Hz, 2H), 3.99 (s, 3H), 4.91 (d, *J* = 17.0 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 5.20 (d, *J* = 10.9 Hz, 3H), 5.34 (d, *J* = 10.7 Hz, 1H), 5.88–6.01 (m, 1H), 6.22–6.33 (m, 1H), 7.47–7.60 (m, 2H), 7.97 (d, *J* = 7.9 Hz, 1H), 8.15 (s, 1H), 8.26 (d, *J* = 8.3 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ (one aromatic carbon is merged with others) 22.2, 26.2, 34.9, 49.0, 52.0, 114.4, 116.7, 118.9, 122.4, 123.4, 123.6, 124.2, 125.2, 125.7, 127.3, 128.9, 133.4, 138.3, 143.3, 148.7, 166.9, 171.3.

**IR** (KBr): 2949, 1760, 1698, 1528, 1435, 1397, 1365, 1207, 1113, 1058 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{23}H_{23}NO_4$ (M = 377.16): C, 73.19; H,

6.14; N, 3.71. Found: C, 72.90; H, 6.20; N, 3.83 %**.**

**MP**: 115–116 °C.

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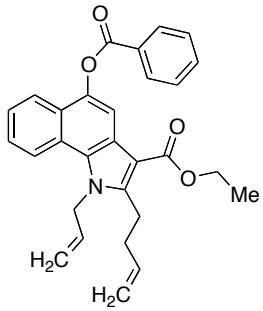
**Ethyl 1-allyl-5-(benzoyloxy)-2-(but-3-enyl)-1*H*-benzo[*g*]indole-3-carboxylate (29):**



**29**

Prepared from compound **25** (351 mg, 1 mmol), benzoyl chloride (280 mg, 2 mmol), yield: 362 mg (80 %) as an off-white solid.

Data of **29**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.49 (t, *J* = 7.1 Hz, 3H), 2.48 (q, *J* = 6.7 Hz, 2H), 3.30–3.36 (m, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.90–5.37 (m, 6H), 5.90–6.05 (m, 1H), 6.22–6.35 (m, 1H), 7.43–7.64 (m, 4H), 7.75 (tt, *J* = 1.3, 8.6 Hz, 1H), 8.03 (dd, *J* = 1.1, 8.2 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 2H), 8.42 (dd, *J* = 1.5, 8.5 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63MHz): δ 15.0, 25.6, 34.3, 48.3, 60.1, 106.4, 113.9, 115.9, 118.1, 121.6, 122.7, 123.0, 123.8, 124.5, 125.2, 126.7, 128.2, 129.1, 130.0, 130.8, 132.9, 134.0, 137.7, 142.8, 147.7, 165.9, 166.2.

**IR** (KBr): 3073, 2981, 1738, 1694, 1527, 1451, 1418, 1247, 1192, 1112, 1087, 1021 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{29}H_{27}NO_4$ (M = 453.19): C, 76.80; H, 6.00; N, 3.09. Found: C, 76.64; H, 5.97; N, 3.26 %.

**MP**: 115–116 °C.

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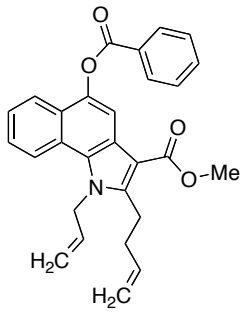
**Methyl 1-allyl-5-(benzoyloxy)-2-(but-3-enyl)-1*H*-benzo[*g*]indole-3-carboxylate (30):**



**30**

Prepared from compound **26** (337 mg, 1 mmol), benzoyl chloride (280 mg, 2 mmol), yield: 359 mg (82 %) as an off-white solid.

Data of **30**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 2.47 (q, *J* = 6.9 Hz, 2H), 3.34 (t, *J* = 7.8 Hz, 2H), 3.98 (s, 3H), 4.94 (d, *J* = 17.2 Hz, 1H), 5.10 (d, *J* = 15.6 Hz, 1H), 5.21 (d, *J* = 15.7 Hz, 3H), 5.35 (d, *J* = 10.6 Hz, 1H), 5.90–6.06 (m, 1H), 6.22–6.36 (m, 1H), 7.44–7.76 (m, 5H), 8.03 (d, *J* = 8.1 Hz, 1H), 8.23–8.31 (m, 2H), 8.40 (d, *J* = 7.4 Hz, 2H).

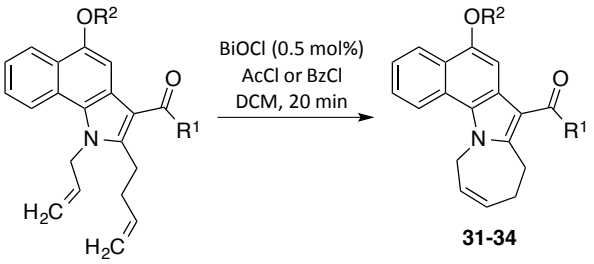
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 25.5, 34.3, 48.4, 51.4, 106.2, 113.9, 116.0, 118.2, 121.7, 122.7, 123.0, 123.6, 124.6, 125.2, 126.7, 128.2, 129.1, 130.0, 130.8, 132.8, 134.1, 137.7, 142.9, 148.1, 166.2, 166.3.

**IR** (KBr): 2930, 1734, 1697, 1623, 1526, 1246, 1192, 1115, 1088, 1068 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{28}H_{25}NO_4$ (M = 439.18): C, 76.52; H, 5.73; N, 3.19. Found: C, 76.31; H, 5.91; N, 3.32 %.

**Mp**: 118–119 °C.

**7.2.7: General procedure for the ring-closing metathesis reaction: Synthesis of 9,12-dihydro-8*H*-azepino[1,2*a*]benzo[*g*] indole derivatives 31-34.**




To a stirred solution of compounds **27-30** (0.5 mmol) in dry dichloromethane (2mL) was added Grubbs 1st generation catalyst (10 mol%) and stirring was continued for 3 h at room temperature under an argon atmosphere. After completion of the reaction the solvent was evaporated and the crude mixture was purified by $Al_2O_3$ (neutral, activity grade II–III) column chromatography using petroleum ether–ethyl acetate mixture (80 : 20, v/v) as eluent.

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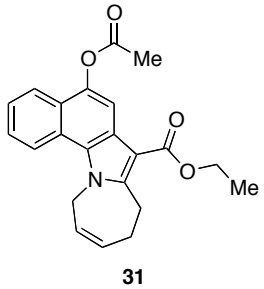
**Ethyl 5-acetoxy-9,12-dihydro-8*H*-azepino[1,2-*a*]benzo[*g*]indole-7-carboxylate (31):**




**31**

Prepared from compound **27** (196 mg, 0.5 mmol), yield: 145 mg (80 %), as an off-white solid. Data of **31**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.44 (t, *J* = 7.1 Hz, 3H), 2.52 (s, 5H), 3.76 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 5.30 (s, 2H), 5.87 (d, *J* = 11.3 Hz, 1H), 6.01 (s, 1H), 7.46–7.60 (m, 2H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 8.32 (d, *J* = 8.3 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63MHz): δ 15.0, 21.5, 23.0, 28.8, 44.3, 60.1, 105.4, 113.9, 121.0, 122.5, 122.8, 123.1, 123.2, 124.4, 125.0, 126.4, 128.2, 134.9, 142.3, 149.9, 166.2, 170.6.

**IR** (KBr): 3436, 3023, 2901, 1762, 1619, 1623, 1542, 1450, 1364, 1204, 1107, 1058 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{22}H_{21}NO_4$ (M = 363.15): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.52; H, 5.90; N, 3.89 %.

**MP**: 138–139 °C.

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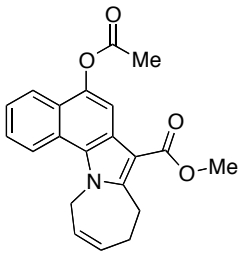
**Methyl 5-acetoxy-9,12-dihydro-8*H*-azepino[1,2-*a*]benzo[*g*]indole-7-carboxylate (32):**




**32**

Prepared from compound **28** (189 mg, 0.5 mmol), yield: 134 mg (77 %) as an off-white solid.

Data of **32**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 2.53 (s, 5H), 3.77 (q, *J* = 5.6 Hz, 2H), 3.99 (s, 3H), 5.31 (d, *J* = 7.3 Hz, 2H), 5.89 (d, *J* = 11.3 Hz, 1H), 6.01 (s, 1H), 7.47–7.61 (m, 2H), 7.97 (d, *J* = 8.1 Hz, 1H), 8.10 (s, 1H), 8.33 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63MHz): δ (one aromatic carbon is merged with others) 21.5, 23.0, 28.8, 44.3, 51.4, 105.2, 113.9, 121.0, 122.5, 122.8, 123.1, 124.5, 125.0, 126.4, 128.2, 134.8, 142.3, 150.0, 166.6, 170.7.

**IR** (KBr): 3430, 3028, 2944, 1753, 1693, 1622, 1543, 1430, 1396, 1365, 1205, 1111, 1059 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{21}H_{19}NO_4$ (M = 349.13): C, 72.19; H, 5.48; N, 4.01. Found: C, 71.84; H, 5.55; N, 4.01 %.

**MP**: 167–168 °C.

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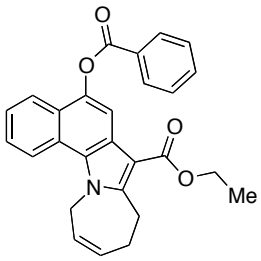
**Ethyl 5-(benzoyloxy)-9,12-dihydro-8*H*-azepino[1,2-*a*]benzo[*g*]indole-7-carboxylate (33):**




**33**

Prepared from compound **29** (227, 0.5 mmol), yield: 164 mg (77%) as an off-white solid.

Data of **33**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.46 (t, *J* = 7.0 Hz, 3H), 2.58 (m, 2H), 3.81 (t, *J* = 6.0 Hz, 2H), 4.44 (q, *J* = 7.0 Hz, 2H), 5.36 (m, 2H), 5.88–5.94 (m, 1H), 6.02–6.09 (m, 1H), 7.43–7.76 (m, 5H), 8.02 (d, *J* = 8.2 Hz, 1H), 8.22 (s, 1H), 8.36–8.42 (m, 3H).

**$^{13}$CNMR** ($CDCl_3$, 63MHz): δ (four aromatic carbons are merged with others) 15.0, 23.0, 28.8, 44.3, 60.1, 105.5, 114.0, 121.0, 122.6, 122.9, 123.3, 124.5, 125.2, 126.4, 128.2, 129.1, 130.0, 130.8, 134.0, 134.9, 142.5, 149.9, 166.2.

**IR** (KBr): 2978, 2926, 1737, 1694, 1623, 1540, 1450, 1402, 1301, 1247, 1179, 1111, 1088 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{23}NO_4$ (M = 425.16): C, 76.22; H, 5.45; N, 3.29. Found: C, 75.97; H, 5.48; N, 3.30 %.

**MP**: 168–169 °C.

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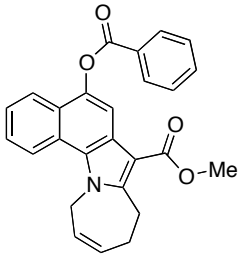
**Methyl 5-(benzoyloxy)-9,12-dihydro-8*H*-azepino[1,2-*a*]benzo-[*g*]indole-7-carboxylate (34):**




**34**

Prepared from compound **30** (220 mg, 0.5 mmol), yield: 156 mg (76 %) as an off-white solid.

Data of **34**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 2.58–2.60 (m, 2H), 3.82 (t, *J* = 6.0 Hz, 2H), 3.96 (s, 3H), 5.36 (d, *J* = 5.0 Hz, 2H), 5.88–5.96 (m, 1H), 6.03–6.11 (m, 1H), 7.43–7.76 (m,

5H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.19 (s, 1H), 8.37–8.42 (m, 3H).

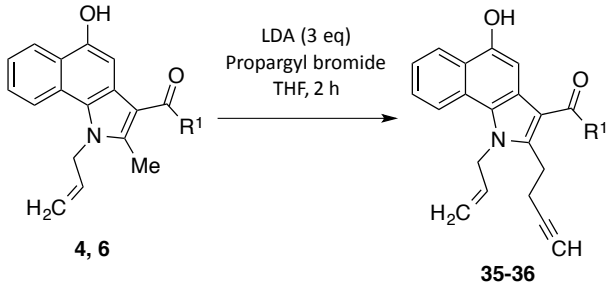
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 23.0, 28.8, 44.3, 51.3, 105.3, 114.1, 121.0, 122.5, 122.9, 123.2, 123.3, 124.5, 125.3, 126.5, 128.2, 129.1, 130.0, 130.8, 134.0, 134.9, 142.6, 150.1, 166.3, 166.6.

**IR** (KBr): 2926, 1734, 1698, 1623, 1601, 1542, 1450, 1396, 1248, 1190, 1114, 1087, 1068, 1020 $cm^{-1}$.

**Elemental anlysis**: Anal. Calcd for $C_{26}H_{21}NO_4$ (M = 413.16): C, 75.90; H, 5.14; N, 3.40. Found: C, 75.64; H, 5.38; N, 3.35 %.

**MP**: 199–200 °C.

### 7.2.7: General procedure for the introduction of propargyl substituents on the C-2 methyl group of 4: Synthesis of compounds 35-36:




A solution of compounds **4** or **6** (1 mmol) in dry THF (4 mL) was added to LDA (3 mmol), prepared from BuLi (3.3 mmol) and diisopropylamine (3 mmol) in dry THF (4 mL), slowly at -20 ◦C and the reaction mixture was stirred for 30 min at the same temperature. Propargyl bromide (2.2 mmol) was then added and stirring was continued for further 2 h. The reaction was quenched by adding saturated NH4Cl solution and extracted with dichloromethane (2 ¥ 10 mL). The organic layer was washed with brine, dried over anhydrous Na2SO4 and the solvent was evaporated. The crude mixture was purified by silica column chromatography eluting with petroleum ether-ethyl acetate mixture (80 : 20, v/v)

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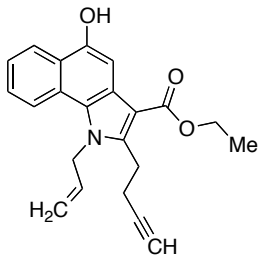
**Ethyl 1-allyl-2-(but-3-ynyl)-5-hydroxy-1*H*-benzo[*g*]indole-3-carboxylate (35):**




Prepared from compound **4** (311 mg, 1 mmol), propargyl bromide (259 mg, 2.2 mmol), yield: 262 mg (75 %) as an off-white solid.

Data of **35**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.50 (t, *J* = 7.1 Hz, 3H), 2.03 (q, *J* = 2.6 Hz, 1H), 2.67 (t, *J* = 7.7 Hz, 2H), 3.43 (t, *J* = 7.5 Hz, 2H), 4.50 (q, *J* = 7.0 Hz, 2H), 4.85 (d, *J* = 17.8 Hz, 1H), 5.32 (s, 3H), 6.22–6.34 (m, 1H), 7.47–7.61 (m, 2H), 7.99 (s, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.9, 19.5, 25.3, 48.5, 60.5, 69.9, 83.6, 102.6, 105.4, 117.9, 120.9, 122.8, 123.6, 123.8, 123.9, 124.9, 125.3, 126.7, 133.0, 144.9, 148.3, 166.5.

**IR** (KBr): 3302, 2982, 1646, 1624, 1600, 1518, 1450, 1334, 1244, 1128, 1074 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{22}H_{21}NO_3$ (M = 349.17): C, 76.06; H, 6.09; N, 4.03. Found: C, 75.86; H, 5.85; N, 4.05 %.

**MP**: 201–202 °C.

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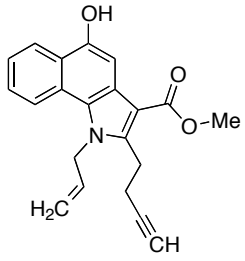
**Methyl 1-allyl-2-(but-3-ynyl)-5-hydroxy-1*H*-benzo[*g*]indole-3-carboxylate (36):**




**36**

Prepared from compound **6** (297 mg, 1 mmol), propargyl bromide (259 mg, 2.2 mmol), yield: 248 mg (74 %) as a pale brown solid.

Data of **36**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 2.02 (s, 1H), 2.66(t, *J* = 7.1 Hz, 2H), 3.43 (t, *J* = 7.3 Hz, 2H), 4.02 (s, 3H), 4.88 (d, *J* = 17.2 Hz, 1H), 5.16–5.33 (m, 3H), 6.23–6.34 (m, 1H), 7.47– 7.60 (m, 2H), 7.90 (s, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.42 (d, *J* = 8.1 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63MHz): δ 19.3, 25.0, 48.6, 51.5, 69.9, 83.6, 102.8, 105.4, 117.9, 121.0, 122.8, 123.6, 123.7, 123.9, 124.6, 125.4, 126.8, 132.9, 145.3, 148.0, 166.7.

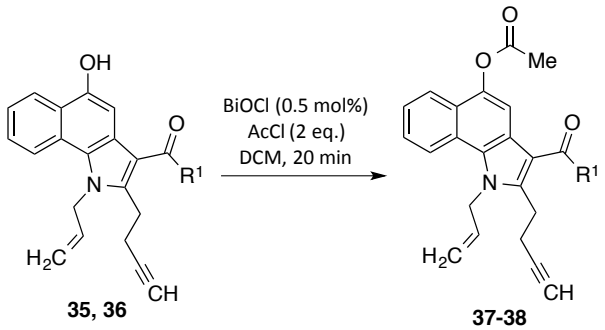
**IR** (KBr): 3299, 2984, 1648, 1624, 1600, 1522, 1449, 1407, 1335, 1244,

1124, 1072 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{21}H_{19}NO_3$ (M = 335.15): C, 75.66; H, 5.74; N, 4.20. Found: C, 75.34; H, 5.92; N, 4.21 %.

**MP**: 160–161 °C.

### 7.2.8: General procedure for the synthesis of compounds 37 and 38.




To a stirred suspension of compound **35** or **36** (1 mmol) and BiOCl (5–10 mol%) in dichloromethane (3 mL) under argon was added acetyl (2 mmol) at room temperature. The reaction was completed in 20 min as indicated by tlc. The mixture was diluted with dichloromethane (10 mL), washed with saturated $NaHCO_3$ solution, water and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and the solvent was evaporated. Purification of the crude mixture by $Al_2O_3$ (neutral, activity grade II-III) column chromatography eluting with petroleum ether–ethyl acetate mixture (85: 15, v/v) gave compounds **37-38**.

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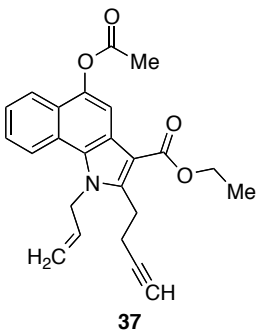
**Ethyl 5-acetoxy-1-allyl-2-(but-3-ynyl)-1*H*-benzo[*g*]indole-3-carboxylate (37):**



**37**

Prepared from compound **35** (349, 1 mmol), acetyl chloride (154, 2 mmol), yield: 363 mg (93 %) as a pale brown viscous liquid.

Data of **37**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.52 (t, *J* = 7.1 Hz, 3H), 2.03 (d, *J* = 2.5 Hz, 1H), 2.55 (s, 3H), 2.70 (t, *J* = 7.2 Hz, 2H), 3.45 (t, *J* = 6.9 Hz, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.90 (d, *J* = 16.7 Hz, 1H),

5.33 (s, 3H), 6.24–6.36 (m, 1H), 7.49–7.59 (m, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.18 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H).

**$^{13}$C NMR** (CDCl3, 63 MHz): δ 13.5, 17.9, 20.0, 23.5, 47.1, 58.8, 68.6, 82.0, 105.2, 112.2, 116.6, 120.2, 121.2, 121.5, 122.1, 123.2, 123.7, 125.3, 126.8, 131.3, 141.3, 144.7, 164.2, 169.1.

**IR** (NaCl): 2984, 1760, 1694, 1625, 1527, 1418, 1366, 1208, 1112 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{24}H_{23}NO_4$ (M = 391.18): C, 74.02; H, 5.95; N, 3.60. Found: C, 73.85; H, 5.88; N, 3.47 %.

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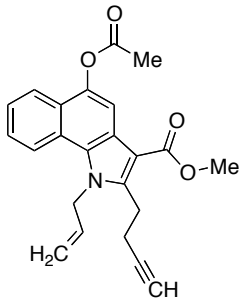
**Methyl 5-acetoxy-1-allyl-2-(but-3-ynyl)-1*H*-benzo[*g*]indole-3-carboxylate (38):**



**38**

Prepared from compound **36** (335 mg, 1 mmol), acetyl chloride (144 mg, 2 mmol), yield: 341 mg (91 %) as an off-white solid.

Data of **38**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 2.01 (t, *J* = 2.6 Hz, 1H), 2.52 (s, 3H), 2.68 (t, *J* = 7.2 Hz, 2H), 3.45 (t, *J* = 7.3 Hz, 2H), 4.00 (s, 3H), 4.90 (d, *J* = 17 Hz, 1H), 5.32–5.35 (m, 3H), 6.22–6.36 (m, 1H), 7.48–7.61 (m, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 8.27 (d, *J* = 8.1 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 19.2, 21.5, 24.8, 48.6, 51.5, 70.1, 83.5, 106.5, 113.7, 118.1, 121.7, 122.7, 122.9, 123.4, 124.7, 125.2, 126.8, 128.3, 132.8, 142.8, 146.5, 166.2, 170.6.

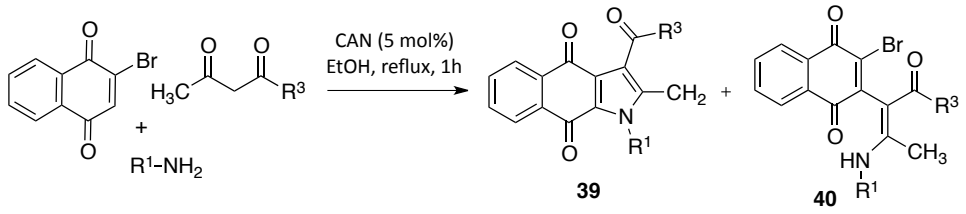
**IR** (KBr): 3294, 2950, 1760, 1698, 1624, 1528, 1435, 1397, 1365, 1268, 1207, 1150, 1115, 1058 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{23}H_{21}NO_4$ (M = 375.15): C, 73.58; H, 5.64; N, 3.73. Found: C, 73.24; H, 5.65; N, 3.98 %.

**MP**: 95–96 °C.

### 7.3: Variations of the Nenitzescu multicomponent reaction.

### 7.3.1: General procedure for the synthesis of indolequinones 39 and the bromoquinone intermediates 40.




To a stirred mixture of the suitable primary amine (1 mmol) and 1,3-dicarbonyl compound (1 mmol) in ethanol (3 mL) was added CAN (5 mol%) and stirring was continued for 30 min at room temperature. 2-Bromo-1,4-naphthoquinone (1 mmol) was then added and the mixture was stirred for 30 min to further time to a room temperature. After completion of the reaction, as indicated by TLC, dichloromethane (20 mL) was added to the mixture and the resulting solution was washed with water (5 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by silica column chromatography using petroleum ether-ethyl acetate mixture as eluent, to give compounds **39** and **40**.

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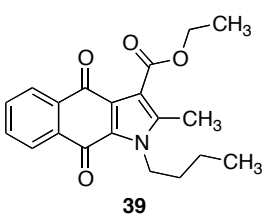
**Ethyl 1-butyl-2-methyl-4,9-dioxo-4,9-dihydro-1*H*-benzo[*f* ]indole-3-carboxylate (39):**



**39**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), butyl amine (73 mg, 1 mmol) and 2-bromo-1,4-naphthoquinone (235 mg, 1 mmol), yield: 183 mg (54 %) as a dark brown viscous liquid.

Data of **39**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.01 (t, *J* = 4.2 Hz, 3H), 1.39–1.54 (m, 5H),

1.70–1.82 (m, 2H), 2.51 (s, 3H), 4.41–4.50 (m, 4H), 7.65–7.72 (m, 2H), 8.11–8.22 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): (two carbon are merged with others) δ 11.2, 14.1, 14.6, 20.4, 32.9, 46.2, 61.6, 114.5, 126.2, 126.6, 127.1, 130.4, 133.3, 133.6, 134.2, 165.2, 176.4, 179.9.

**IR** (NaCl): 2960, 2931, 2865, 1706, 1652, 1273 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd. for $C_{20}H_{21}NO_4$ (M = 339.15): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.53; H, 5.98; N, 3.81 %.

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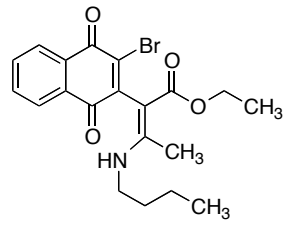
**(*E*)-Ethyl 2-(3-bromo-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3 (butyl amino)but-2-enoate (40):**




**40**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), butylamine (73 mg, 1 mmol), 2-bromo-1,4-naphthoquinone (235 mg, 1 mmol), yield (%): 50 mg (18 %) as a pale brown solid.

Data of **40**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H), 1.40–1.55 (m, 2H), 1.61–1,72 (m, 2H), 1.87 (s, 3H), 3.32 (q, *J* = 6.7 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 7.73–7.81 (m, 2H), 8.13–8.23 (m, 2H), 9.67 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.2, 14.8, 17.4, 20.5, 32.4, 43.7, 59.6, 90.9, 124.6, 127.7, 127.8, 131.9, 132.5, 134.0, 134.4, 150.1, 161.6, 168.1, 179.1, 182.8.

**IR** (KBr): 2962, 2929, 1682, 1599, 1464, 1382, 1278, 1242, 1160 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd. for $C_{20}H_{22}BrNO_4$ (M = 419.07): C, 57.15; H, 5.28; N, 3.33. Found: C, 57.07; H, 5.20; N, 3.52 %.

**MP**: 98–99 °C.

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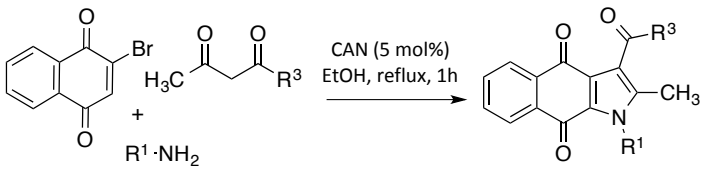
### 7.3.2: General procedure for the synthesis of indolequinones 39, 41-44.

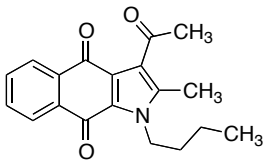



**39, 41-44**

| Compd | $R^1$ | $R^2$ |
|---|---|---|
| **39** | *n*-Bu | OEt |
| **41** | *n*-Bu | Me |
| **42** | $CH_2$-Ph | Me |
| **43** | $CH_2$-CH=$CH_2$ | Me |
| **44** | $CH_2$-C≡CH | Me |

To a stirred mixture of primary amines (1 mmol) and 1,3-dicarbonyl compounds (1 mmol) in ethanol (3 mL) was added CAN (5 mol%) and stirred was continued for 30 min at room temperature. 2-bromo-1,4-naphthoquinone (1 mmol) was then added and the mixture was refluxed for 30 min to further time. After completion of the reaction, as indicated by TLC, dichloromethane (20 mL) was added to the mixture and the resulting solution was washed with water (5 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by silica column chromatography using a petroleum ether-ethyl acetate mixture as eluent, to give the expected compounds.

**3-Acetyl-1-butyl-2-methyl-1*H*-benzo[*f* ]indole-4,9-dione (41):**



**41**

Prepared from acetyl acetone (100 mg, 1 mmol), butyl amine (73 mg, 1 mmol), 2-bromo-1,4-naphthoquinone (235 mg, 1 mmol), yield: 207 mg (67 %), as a pale yellow solid.

Data of **41**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 0.86 (t, *J* =7.3Hz, 3H), 1.25–1.40 (m, 2H), 1.55–1.67 (m, 2H), 2.29 (s, 3H), 2.58 (s, 3H), 4.32 (t, *J* = 7.5 Hz, 2H), 7.55 (dd, *J* = 3.3, 5.7 Hz, 2H), 7.98 (dd, *J* = 3.2, 5.8 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63MHz): δ 11.2, 14.2, 20.5, 30.1, 32.1, 32.8, 46.1, 123.2, 125.6, 126.7, 127.0, 129.9, 133.6, 133.7, 133.9, 141.6, 176.4, 181.1, 199.8;

**IR** (KBr): 2960.8, 2930, 2870, 1652, 1592, 1495, 1469, 1433, 1354, 1269, 1210, 1096, 1000 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{19}H_{19}NO_3$ (M = 309.14): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.57; H, 6.32; N, 4.15 %.

**MP**: 115–116 °C.

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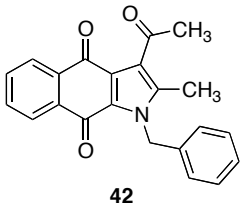
**3-Acetyl-1-benzyl-2-methyl-1*H*-benzo[*f* ]indole-4,9-dione (42):**



**42**

Prepared from acetyl acetone (100 mg, 1 mmol), benzyl amine (107 mg, 1 mmol), 2-bromo-1,4-naphthoquinone (235 mg, 1 mmol), yield: 174 mg (51 %), as a yellow solid.

Data of **42**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 2.39 (s, 3H), 2.76 (s, 3H), 5.86 (s, 3H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.29–7.38 (m, 3H), 7.70–7.74 (m, 2H), 8.12–8.20 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 11.3, 32.1, 49.2, 123.5, 125.7, 126.6, 126.8, 127.1, 128.2, 129.4, 130.2, 133.6, 133.7, 133.8, 133.9, 135.9, 142.4, 176.6, 181.1,

199.6.

**IR** (NaCl): 1651, 1591, 1496, 1269 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd. for $C_{22}H_{17}NO_3$ (M = 343.12): C, 76.95; H, 4.99; N, 4.08. Found: C, 76.72; H, 4.82; N, 4.01 %.

**MP**: 163–164 °C.

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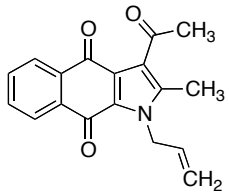
**3-Acetyl-1-allyl-2-methyl-1*H*-benzo[*f* ]indole-4,9-dione (43):**



**43**

Prepared from acetyl acetone (100 mg, 1 mmol), allyl amine (57 mg, 1 mmol), 2-bromo-1,4-naphthoquinone (235 mg, 1 mmol), yield: 128 mg (44), as a yellow solid.

Data of **43**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 2.42 (s, 3H), 2.74 (s, 3H), 4.97 (d, *J* = 17.1 Hz, 1H), 5.21 (t, *J* = 12.3 Hz, 3H), 5.94–6.09 (m, 1H), 7.69 (m, 2H), 8.10–8.16 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 10.9, 32.1, 48.0, 117.6, 123.2, 125.5, 126.7, 127.0, 129.9, 132.2, 133.5, 133.6, 133.7, 133.9, 142.1, 176.4, 181.0, 199.6.

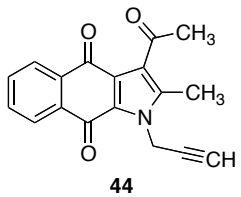
**IR** (NaCl): 1652, 1591, 1496, 1430, 1270, 1210 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd. for $C_{18}H_{15}NO_3$ (M = 293.11): C, 73.71; H, 5.15; N, 4.78. Found: C, 73.45; H, 5.06; N, 4.68 %.

**MP**: 117–118 °C.

---

**3-Acetyl-2-methyl-1-(prop-2-ynyl)-1*H*-benzo[*f* ]indole-4,9-dione (44):**



**44**

Prepared from acetyl acetone (100 mg, 1 mmol), propargyl amine (55 mg, 1 mmol), 2-bromo-1,4-naphthoquinone (235 mg, 1 mmol), yield: 122 mg (42 %), as a yellow solid.

Data of **44**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 2.40 (t, *J* = 2.3 Hz, 1H), 2.55 (s, 3H), 2.75 (s, 3H), 5.44 (d, *J* = 2.3 Hz, 2H), 7.71–7.77 (m, 2H), 8.15–8.20 (m, 2H).

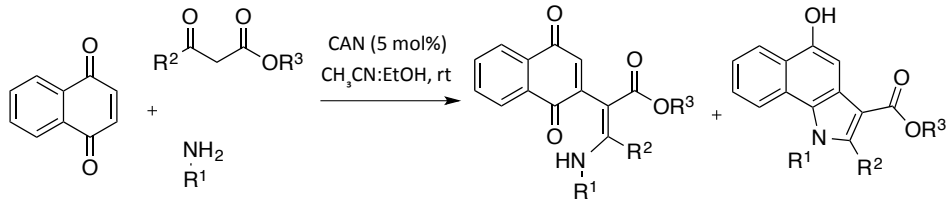
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ (one quaternary carbon merged) 10.6, 31.6, 34.8, 73.5, 121.1, 122.8, 125.1, 126.2, 126.6, 128.8, 132.8, 133.2, 133.4, 141.6, 176.1, 180.4, 198.8.

**IR** (NaCl): 1668, 1653, 1592, 1494, 1267, 1210, 1104 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd. for $C_{18}H_{13}NO_3$ (M = 291.09): C, 74.22, H, 4.50, N, 4.81; Found: C, 73.92, H, 4.39, N, 4.78 %.

**MP**: 194–195 °C.

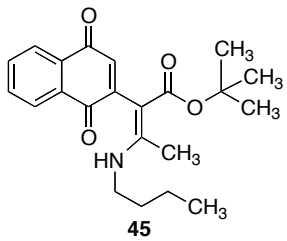
### 7.3.3: General procedure for the synthesis of quinones 1 and 45-51.




| Compd | $R^1$ | $R^2$ | $R^3$ | Time, h | IV/III ratio[a] | Yield of IV (%)[b] |
|---|---|---|---|---|---|---|
| **1** | *n*-Bu | Me | Et | 1.5 | 85:15 | 65 |
| **45** | *n*-Bu | Me | $^t$Bu | 1 | 80:20 | 68 |
| **46** | $CH_2$-CH=$CH_2$ | Me | Et | 1 | 75:25 | 62 |
| **47** | *n*-Bu | Me | Me | 1.51 | 75:25 | 60 |
| **48** | *n*-Bu | Me | $CH_2$-CH=$CH_2$ | 1.5 | 78:22 | 65 |
| **49** | *n*-Pr | Me | Et | 1 | 70:30 | 58 |
| **50** | $CH_2$-Ph | Me | Et | 1.5 | 65:35 | 62 |
| **51** | *n*-Bu | n-Pr | Et | 1 | 65:35 | 60 |

A solution of the suitable β-ketoester (1 mmol), the suitable primary amine (1 mmol) and CAN (5 mol %) in acetonitrile (0.5 mL) was stirred at room temperature for 30 min. A solution of 1,4-naphthoquinone (158 mg, 1 mmol) in EtOH (110 mL) was added, and stirring at room temperature was continued for 30 min. Thereafter, the reaction mixture was diluted with water (3 mL) and extracted with dichloromethane. The combined organic phases were evaporated to dryness, and then flash column chromatography eluting with petroleum ether/ethyl acetate purified the crude product. Characterization data for the major products **1, 45-51** are given below.

**(*E*)-tert-Butyl 3-(butylamino)-2-(1,4-dioxo-1,4-dihydronaphth-2-yl)but-2-enoate (45):**



**45**

Prepared from *tert*-butyl acetoacetate (158 mg, 1 mmol), butyl amine (73, 1 mmol), 1,4-naphthoquinone (158 mg, 1 mmol), yield: 250 mg (65 %) as a dark red viscous liquid.

Data of **45**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 9H), 1.48-1.52 (m, 2H), 1.60-1.69 (m, 2H), 1.99 (s, 3H), 3.29 (q, *J* = 6.8 Hz, 2H), 6.68 (s, 1H), 7.72-7.76 (m, 2H), 8.08-8.14 (m, 2H), 9.73 (s, 1H).

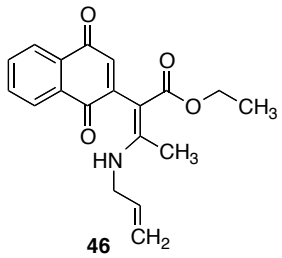
**$^{13}$C NMR** ($CDCl_3$, 63MHz): δ 14.2, 17.4, 20.5, 28.6, 32.5, 43.8, 79.8, 91.6, 126.1, 127.0, 132.7, 133.5, 133.6, 133.7, 136.2, 150.3, 161.4, 169.0, 186.0. 186.3.

**IR** (NaCl): 2973, 2932, 1691, 1665, 1596, 1547, 1529, 1501, 1460, 1390, 1066 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{22}H_{27}NO_4$ (M = 369.19): C, 71.52, H, 7.37, N, 3.79; found: C, 71.27, H, 7.09, N, 3.53 %

---

**(*E*)-Ethyl 3-(allylamino)-2-(1,4-dioxo-1,4-dihydronaphth-2-yl)but-2-enoate (46):**



**46**

Prepared from ethylacetoacetate (130 mg, 1 mmol), allyl amine (57 mg, 1 mmol), 1,4-naphthoquionone (158 mg, 1 mmol), yield: 201 mg (62 %) as a dark red viscous liquid.

Data of **46**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.12 (t, *J* = 7.1 Hz, 3H), 1.96 (s, 3H), 3.93-3.98 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 5.23-5.36 (m, 2H),

5.86-5.99 (m, 1H), 6.77 (s, 1H), 7.74-7.77 (m, 2H), 8.10-8.14 (m, 2H), 9.86 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 17.2, 46.1, 59.7, 90.5, 117.1, 126.2, 127.2, 132.8, 133.2, 133.7, 133.9, 134.2, 137.8, 149.2, 161.9, 169.1, 185.7, 186.0.

**IR** (NaCl): 2981, 1649, 1593, 1300, 1252, 1220 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{19}H_{19}NO_4$ (M = 325.13): C, 70.14, H, 5.89, N, 4.31; found: C, 69.85, H, 6.04, N, 3.88 %.

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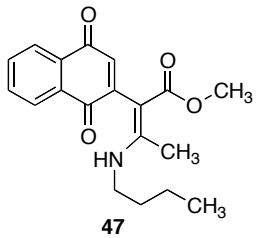
**(*E*)-Methyl 3-(butylamino)-2-(1,4-dioxo-1,4-dihydro-naphth-2-yl)but-2-enoate (47):**




**47**

Prepared from acetylacetone (100 mg, 1 mmol), butyl amine (73 mg, 1 mmol), 1,4-naphthoquinone (158 mg, 1 mmol), yield: 196 mg (60 %) as a dark red viscous liquid.

Data of **47**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.40-1.55 (m, 2H), .61-1.72 (m, 2H), 1.96 (s, 3H), 3.32 (q, *J* = 6.8 Hz, 2H), 3.58 (s, 3H), 6.78 (s, 1H), 7.72-7.79 (m, 2H), 8.10-8.15 (m, 2H), 9.78 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.2, 17.5, 20.5, 32.3, 43.7, 51.1, 89.1, 126.2, 127.3, 132.8, 133.1, 133.8, 133.9, 138.0, 149.0, 162.2, 169.6, 185.7, 186.0.

**IR** (NaCl): 2954, 1650, 1592, 1439, 1323, 1299, 1259, 1220, 1143, 1069, 1015 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{19}H_{21}NO_4$ (M = 327.15): C, 69.71, H, 6.47, N, 4.28; found: C, 69.58, H, 6.41, N, 4.19 %.

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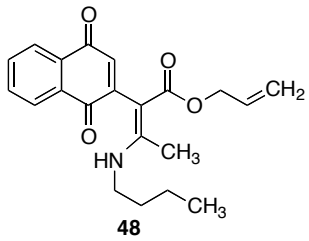
**(*E*)-Allyl 3-(butylamino)-2-(1,4-dioxo-1,4-dihydronaphth-2-yl)but-2-enoate (48):**



**48**

Prepared from allyl acetoacetate (142, 1 mmol), butyl amine (73 mg, 1 mmol), 1,4-napthoquinone (158 mg, 1 mmol), yield: 229 mg (65 %) as a dark red viscous liquid.

Data of **48**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.40-1.54 (m, 2H), 1.60-1.71 (m, 2H), 1.97 (s, 3H), 3.32 (q, *J* = 6.8 Hz, 2H), 4.51-4.54 (m, 2H), 5.06-5.18 (m, 2H), 5.74-5.89 (m, 1H), 6.79 (s, 1H), 7.73-7.77 (m, 2H), 8.10-8.14 (m, 2H), 9.77 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.2, 17.6, 20.5, 32.3, 43.8, 64.2, 89.2, 117.0, 126.2, 127.3, 132.7, 133.2, 133.3, 133.8, 133.9, 137.9, 149.1, 162.4, 168.7, 185.8, 186.0.

**IR** (NaCl): 2926, 2339, 1650, 1592, 1455, 1324, 1298, 1252, 1142, 1055, 1015, 992 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{21}H_{23}NO_4$ (M = 353.16): C, 71.37; H, 6.56; N, 3.96; found: C, 71.06; H, 6.31; N, 3.87.

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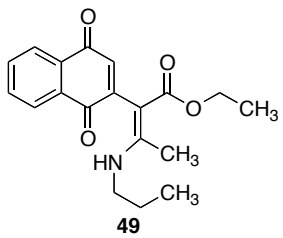
**(*E*)-Ethyl 2-(1,4-dioxo-1,4-dihydronaphth-2-yl)-3-propyl-aminobut-2-enoate (49):**



**49**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), propyl amine (59 mg, 1 mmol), 1,4-naphthoquinone (158 mg, 1 mmol), yield: 189 mg (58 %) as a dark red viscous liquid.

Data of **49**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.02-1.15 (m, 6H), 1.63-1.75 (m, 2H), 1.98 (s,

3H), 3.30 (q, *J* = 6.9 Hz, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 6.76 (s, 1H), 7.73-7.77 (m, 2H), 8.09-8.14 (m, 2H), 9.81 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 11.9, 14.7, 17.5, 23.6, 45.7, 59.6, 89.7, 126.2, 127.2, 132.8, 133.3, 133.7, 133.8, 137.5, 149.4, 162.0, 169.2, 185.9, 186.0.

**IR** (NaCl): 2966, 2362, 1646, 1593, 1458, 1323, 1298, 1259, 1221, 1142, 1064, 1018 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{19}H_{21}NO_4$ (M = 327.15): C, 69.71; H, 6.47; N, 4.28; found: C, 69.92; H, 6.29; N, 4.07.

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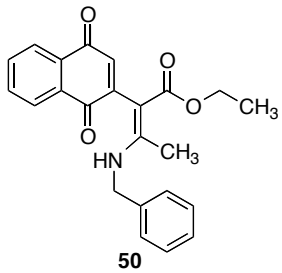
**(*E*)-Ethyl 3-(benzylamino)-2-(1,4-dioxo-1,4-dihydro-naphth-2-yl)but-2-enoate (50):**




**50**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), benzyl amine (107 mg, 1 mmol), 1,4-naphthoquinone (158 mg, 1 mmol), yield: 232 mg (62 %) as a dark red viscous liquid.

Data of **50**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.12 (t, *J* = 7.1 Hz, 3H), 1.98 (s, 3H), 4.07 (q, *J* = 7.1 Hz, 2H), 4.55 (d, *J* = 5.8 Hz, 2H), 6.78 (s, 1H), 7.29-7.44 (m, 5H), 7.74-7.78 (m, 2H), 8.10-8.15 (m, 2H), 10.11 (s, 1H).

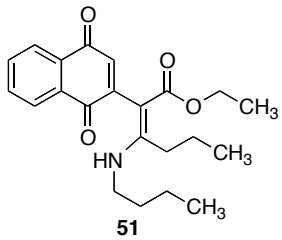
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6,17.6, 47.8, 59.8, 90.9, 126.3, 127.2, 127.3, 128.0, 129.3, 132.7, 133.2, 133.8, 133.9, 137.8, 138.1, 149.1, 161.8, 169.1, 185.7, 186.0.

**IR** (NaCl): 3272, 1645, 1594, 1448, 1414, 1299, 1258, 1220, 1098 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{23}H_{21}NO_4$ (M = 375.15): C, 73.58; H, 5.64; N, 3.73; found: C, 73.26; H, 5.36; N, 3.42.

---

**(*E*)-Ethyl 3-(butylamino)-2-(1,4-dioxo-1,4-dihydronaphth-2-yl)hex-2-enoate (51):**



**51**

Prepared from ethyl 3-oxohexanoate (158 mg, 1 mmol), butyl amine (73 mg, 1 mmol), 1,4-naphthoquinone (158 mg, 1 mmol), yield: 221 mg (60 %) as a dark red viscous liquid.

Data of **51**:

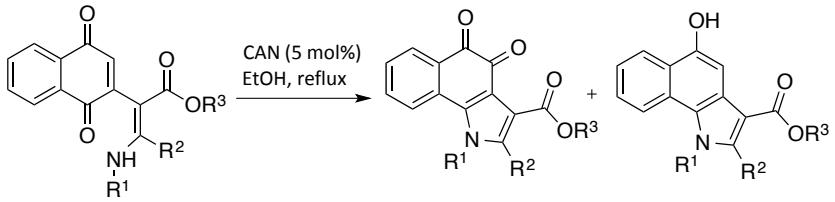
**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 0.86-1.01 (m, 6H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.40-1.55 (m, 4H), 1.60-1.72 (m, 2H), 2.19-2.25 (m, 2H), 3.30 (q, *J* = 6.8 Hz, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 6.80 (s, 1H), 7.73-7.77 (m, 2H), 8.10-8.14 (m, 2H), 9.69 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.2, 14.6, 14.7, 20.5, 22.2, 32.2, 32.6, 43.3, 59.6, 89.2, 126.2, 127.2, 132.7, 133.2, 133.7, 133.9, 137.3, 149.5, 165.4, 169.4, 186.0, 186.1.

**IR** (**neat**): 2961, 2932, 2873, 1667, 1649, 1595, 1665, 1363, 1324, 1253, 1142, 1028 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{22}H_{27}NO_4$ (M = 369.19): C, 71.52; H, 7.37; N, 3.79; found: C, 71.44; H, 7.24; N, 3.59.

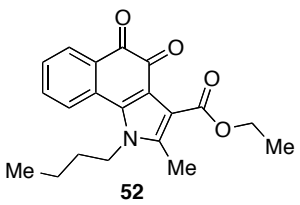
### 7.3.4: General procedure: Synthesis of compounds 52-59




| Compd | $R^1$ | $R^2$ | $R^3$ | Time, h |
|---|---|---|---|---|
| **52** | *n*-Bu | Me | Et | 2 |
| **53** | *n*-Bu | Me | $^t$Bu | 1 |
| **54** | $CH_2$-CH=$CH_2$ | Me | Et | 2 |
| **55** | *n*-Bu | Me | Me | 0.5 |
| **56** | *n*-Bu | Me | $CH_2$-CH=$CH_2$ | 1 |
| **57** | *n*-Pr | Me | Et | 2 |
| **58** | $CH_2$-Ph | Me | Et | 2 |
| **59** | *n*-Bu | *n*-Pr | Et | 1 |

A suspension of the suitable quinone (0.5 mmol) and CAN (5 mol %) in EtOH (1.5 mL) was refluxed for the time indicated in the below table. After the disappearance of starting material, as indicated by TLC, the reaction mixture was diluted with water (5 mL) and extracted with dichloromethane. The combined organic layers were evaporated under reduced pressure and crude residue thus obtained was purified by silica gel column chromatography, eluting with 20% petroleum ether/ethyl acetate. Characterization data for compounds **52-59** are given below.

**Ethyl 1-butyl-2-methyl-4,5-dioxo-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (52):**



**52**

Prepared form compound **1** (170 mg, 0.5 mmol) and isolated as a purple solid.

Data of **52**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.04 (t, *J* = 7.1 Hz, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.47-1.61 (m, 2H), 1.81-1.61 (m, 2H), 2.47 (s, 3H), 4.19 (t, *J* = 8.0 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 7.32-7.39 (m, 1H), 7.54-7.60 (m, 2H), 8.10 (d, *J* = 8.4 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 11.3, 14.0, 14.5, 20.3, 32.2, 46.5, 61.4, 115.2, 120.5, 122.7, 128.6, 130.3, 130.7, 131.8, 135.5, 136.6, 139.6, 165.4, 174.4, 182.6.

**IR** (NaCl): 2961, 2931, 2873, 1693, 1666, 1650.3, 1594, 1548, 1503, 1469, 1302, 1223, 1127, 1021 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{20}H_{21}NO_4$ (M = 339.15): C, 70.78; H, 6.24; N, 4.13; found: C, 70.93; H, 6.28; N, 4.18.

**Mp**: 112-113 °C.

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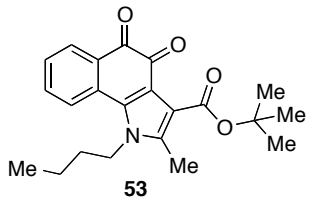
***tert*-Butyl 1-butyl-2-methyl-4,5-dioxo-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (53):**



**53**

Prepared from compound **45** (184 mg, 0.5 mmol) and isolated as a red solid.

Data of **53**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.07 (t, *J* = 7.2 Hz, 3H), 1.47-1.59 (m, 2H), 1.64 (s, 9H), 1.80-1.93 (m, 2H), 2.45 (s, 3H), 4.17 (t, *J* = 8.1 Hz, 2H), 7.32-7.38 (m, 1H), 7.53-7.63 (m, 2H), 8.11 (d, *J* = 8.5 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 11.1, 14.0, 20.3, 28.4, 31.3, 32.2, 46.4, 82.2, 117.0, 122.6, 128.5, 130.3, 130.8, 131.8, 135.5, 136.2, 138.8, 164.8, 174.0, 182.5.

**IR** (NaCl): 2996, 1691, 1660, 1593, 1502, 1462, 1366, 1321, 1278, 1153,

1132, 1066 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{22}H_{25}NO_4$ (M = 367.18): C, 71.91; H, 6.86; N, 3.81; found: C, 71.69; H, 6.68; N, 3.98.

**Mp**: 145-146 °C.

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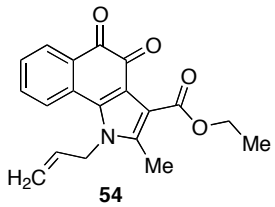
**Ethyl 1-allyl-2-methyl-4,5-dioxo-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (54):**



**54**

Prepared from compound **46** (162, 0.5 mmol) and isolated as a red solid.

Data of **54**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.43 (t, *J* = 7.1 Hz, 3H), 2.45 (s, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.87 (br-s, 2H), 5.11 (d, *J* = 17.1 Hz, 1H), 5.46 (d, *J* = 10.4 Hz, 1H), 6.10-6.23 (m, 1H), 7.28e7.41 (m, 1H), 7.54-7.56 (m, 2H), 8.11 (d, *J* = 7.6 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 10.8, 14.5, 48.7, 61.5, 115.2, 118.8, 120.2, 123.3, 128.8, 130.2, 130.3, 131.0, 131.6, 135.4, 137.9, 140.4, 165.2, 174.6, 182.8.

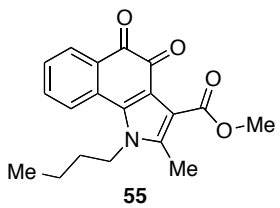
**IR** (NaCl): 2918, 2850, 1709, 1666, 1594, 1548, 1492.9, 1462, 1407, 1302, 1273, 1228, 1139, 1069 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{19}H_{17}NO_4$ (323.12): C, 70.58; H, 5.30; N, 4.33; found: C, 70.36; H, 5.48; N, 4.11.

**Mp**: 114-115 °C.

---

**Methyl 1-butyl-2-methyl-4,5-dioxo-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (55):**



**55**

Prepared from compound **47** (163, 0.5 mmol), and isolated as a red solid.

Data of **55**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.08 (t, *J* = 7.2 Hz, 3H), 1.50-1.59 (m, 2H), 1.83-1.95 (m, 2H), 2.49 (s, 3H), 3.92 (s, 3H), 4.21 (t, *J* = 7.7 Hz, 2H), 7.34-7.38 (m, 1H), 7.40-7.62 (m, 2H), 8.12 (d, *J* = 8.2 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 11.3, 14.0. 20.3, 32.2, 46.5, 52.4, 114.7, 120.6, 122.7, 128.7, 130.4, 130.7, 131.8, 135.5, 136.7, 139.9, 165.7, 174.7, 182.7.

**IR** (NaCl): 2958, 2873, 1710, 1666, 1650, 1594, 1548, 1536, 1502, 1468, 1442, 1402, 1312, 1223, 1126 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{19}H_{19}NO_4$ (325.13): C, 70.14; H, 5.89; N, 4.31; found: C, 69.96; H, 5.90; N, 4.44.

**Mp**: 125-126 °C.

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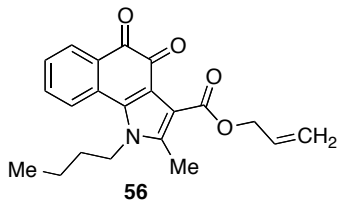
**Allyl 1-butyl-2-methyl-4,5-dioxo-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (56):**



**56**

Prepared from compound **48** (176 mg, 0.5 mmol), and isolated as a red solid.

Data of **56**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.07 (t, *J* = 7.3 Hz, 3H), 1.50-1.63 (m, 2H), 1.82-1.94 (m, 2H), 2.48 (s, 3H), 4.20 (t, *J* = 7.8 Hz, 2H), 4.83-4.86 (m, 2H), 5.29 (dd, *J* = 10.3, 1.4 Hz, 1H), 5.44 (dd, *J* = 17.2, 1.4, 1H), 6.03-6.19 (m, 1H), 7.30-7.40 (m, 1H), 7.55-7.61 (m, 2H), 8.12 (d, *J* = 7.7 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 11.3, 14.0, 20.3, 32.2, 46.5, 66.2, 114.7, 119.0, 120.5, 122.7, 128.6, 130.3, 130.6, 131.7, 132.6, 135.5, 136.7, 140.1, 165.0, 174.4, 182.5.

**IR** (NaCl): 2959, 1701, 1666, 1593, 1499, 1466, 1267, 1126 cm_1;

**Elemental analysis**: Anal. Calcd for $C_{21}H_{21}NO_4$ (M = 351.15): C, 71.78; H,

6.02; N, 3.99; found: C, 71.63; H, 6.26; N, 4.19.

**Mp**: 145-146 °C.

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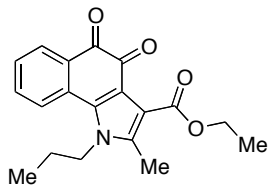
**Ethyl 2-methyl-4,5-dioxo-1-propyl-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (57):**



**57**

Prepared from compound **49** (163 mg, 0.5 mmol) and isolated as a purple solid.

Data of **57**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.13 (t, *J* = 7.4 Hz, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.89-1.99 (m, 2H), 2.49 (s, 3H), 4.17 (dd, *J* = 6.3, 8.1 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 7.34-7.40 (m, 1H), 7.53-7.61 (m, 2H), 8.13 (dd, *J* = 7.7, 1.4 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 11.3, 11.4, 14.5, 23.6, 48.0, 61.4, 115.2, 120.5, 122.6, 128.6, 130.3, 130.7, 131.8, 135.5, 136.6, 139.6, 165.3, 174.4, 182.6.

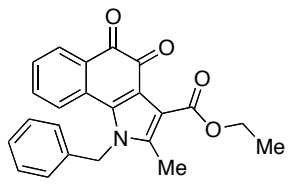
**IR** (NaCl): 3014, 2925, 2853, 1697, 1666, 1595, 1536, 1501, 1465, 1366, 1271, 1128, 1020 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{19}H_{19}NO_4$ (325.13): C, 70.14; H, 5.89; N, 4.31; found: C, 70.30; H, 5.52; N, 4.08.

**Mp**: 79-80 °C.

---

**Ethyl 1-benzyl-2-methyl-4,5-dioxo-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (58):**



**58**

Prepared from compound **50** (187 mg, 0.5 mmol) and isolated as a red solid.

Data of **58**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.45 (t, *J* = 7.1 Hz, 3H), 2.41 (s, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 5.51 (s, 2H), 7.17 (d, *J* = 6.6 Hz, 2H),

7.27-7.45 (m, 6H), 8.08-8.11 (m, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 11.1, 14.5, 50.1, 61.5, 115.3, 120.4, 123.2, 125.7, 128.7, 128.8, 130.0, 130.1, 130.2, 131.6, 134.7, 135.5, 138.0, 140.6, 165.1, 174.4, 182.5.

**IR** (NaCl): 2981, 2928, 1710, 1666, 1594, 1494, 1462, 1302, 1203 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{23}H_{19}NO_4$ (M = 373.13): C, 73.98; H, 5.13; N, 3.75; found: C, 73.78; H, 5.35; N, 3.41.

**Mp**: 200-201 °C.

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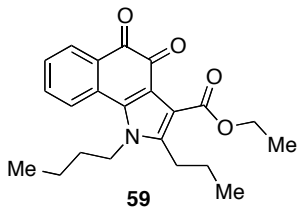
**Ethyl 1-butyl-4,5-dioxo-2-propyl-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (59):**



**59**

Prepared from compound **51** (184 mg, 0.5 mmol) and isolated as a red solid.

Data of **59**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.02-1.10 (m, 6H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.50-1.59 (m, 2H), 1.62-1.71 (m, 2H), 1.81-1.94 (m, 2H), 2.82 (t, *J* = 7.7 Hz, 2H), 4.20 (t, *J* = 8.0 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 7.33-7.40 (m, 1H), 7.59-7.61 (m, 2H), 8.13 (d, *J* = 8.4 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.0, 14.3, 14.5, 20.3, 23.7, 27.0, 32.8, 46.2, 61.4, 115.2, 120.8, 122.7, 128.6, 130.4, 130.9, 131.8, 135.5, 136.4, 143.6, 165.3, 174.5, 182.6.

**IR** (NaCl): 2962, 2933, 2873, 1711, 1667, 1594, 1502, 1466, 1308, 1218, 1126, 1024 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{22}H_{25}NO_4$ (M = 367.18): C, 71.91; H, 6.86; N, 3.81; found: C, 71.69; H, 6.72; N, 3.90.

**Mp**: 114-115 °C.

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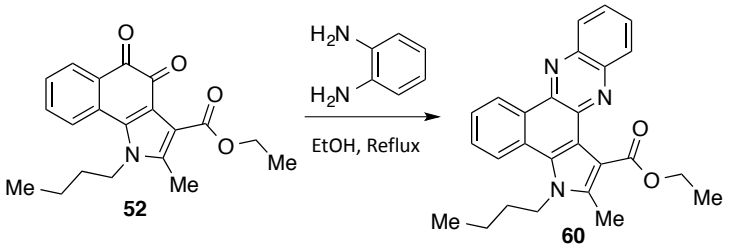
### 7.3.5: Synthesis of ethyl 3-butyl-2-methyl-3*H*-benzo[*a*]pyrrolo[2,3-c]phenazine-1-carboxylate (60).




To a solution of compound **52** (339 mg, 1 mmol) in ethanol (5 mL) was added *o*-phenylenediamine (108 mg, 1 mmol). The resulting solution was refluxed for 1 h, cooled and a mixture of water (10 mL) and ethyl acetate (15 mL) was added. The aqueous phase was extracted with additional ethyl acetate. The combined extracts were dried over $Na_2SO_4$ and evaporated to yield 370 mg (90%) of compound **60**, as a yellow solid.

Data of **60**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.09 (t, *J* = 7.2 Hz, 3H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.56-1.65 (m, 2H), 1.95-2.07 (m, 2H), 2.65 (s, 3H), 4.53 (t, *J* = 7.5 Hz, 2H), 4.66 (q, *J* = 7.1 Hz, 2H), 7.66-7.83 (m, 4H), 8.17-8.24 (m, 2H), 8.31-8.35 (m, 1H), 9.60 (dd, *J* = 8.0, 1.4 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 11.8, 14.2,14.5,14.9, 20.5, 23.1, 29.7, 30.0, 30.1, 32.3, 32.6, 46.6, 61.5,121.0, 125.7, 126.6, 127.8, 128.7, 129.9, 130.1, 130.2, 140.9, 168.5.

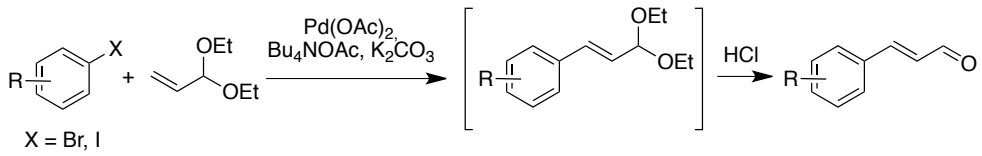
**IR** (NaCl): 2957, 2921, 2855, 1712, 1577, 1544, 1508, 1463, 1412, 1343, 1277, 1232, 1172, 1121, 1071, 1020 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{26}H_{25}N_3O_2$ (M = 411.19): C, 75.89; H, 6.12; N, 10.21; found: C, 75.63; H, 6.03; N, 10.05.

**Mp**: 167 °C.

## 7.4: Multicomponent synthesis of arenoquinolizines from acyclic precursors

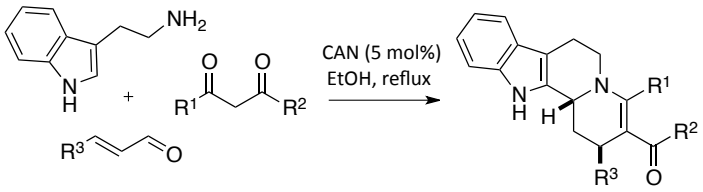
### 7.4.1: Preparation of starting materials derived from cinnamaldehyde: General procedure[141]



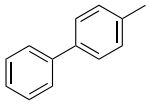
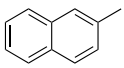

To a stirred solution of the suitable aryl iodide or bromide (0.5 mmol) in 2.0 mL of DMF were added acrolein diethyl acetal (1.5 mmol), tetrabutylammonium acetate (1.0 mmol), potassium carbonate (0.75 mmol), potassium chloride (0.5 mmol), and palladium acetate (0.015 mmol). The mixture was stirred for 1.5 h at 90 °C and cooled. 2 M HCl (5 mL) was slowly added and the resulting mixture was stirred at room temperature for 10 min. Then, the mixture was extracted with ether (3 x 10 mL), and the combined extracts were washed with water (5 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with *n*-hexane/ethyl acetate as eluent to give the target cinnamaldehyde derivatives.

[141] Gianfranco, B.; Sandro, C.; Giancarlo, F. *Org. Lett*. **2003**, *5*, 777.

## 7.4.2. General procedure for the synthesis of indolo[2,3-*a*]quinolizines 62-78




**62-76**

| Compd | $R^1$ | $R^2$ | $R^3$ | t (h) |
|---|---|---|---|---|
| **62** | Me | OEt | Ph | 1.5 |
| **63** | Me | OMe | Ph | 1 |
| **64** | Me | OEt |  | 1.5 |
| **65** | Me | OEt | 4-$ClC_6H_4$ | 1.5 |
| **66** | Me | OEt | 4-$MeOC_6H_4$ | 1.5 |
| **67** | Me | OEt | 2-$NO_2C_6H_4$ | 1.5 |
| **68** | Me | OEt |  | 1 |
| **69** | Me | OEt |  | 1 |
| **70** | Me | OEt | Me | 1 |
| **71** | Me | OEt | *n*-Pr | 1 |
| **72** | Me | S-$^t$Bu | Ph | 1 |
| **73** | Me | O-$^t$Bu | Ph | 1 |
| **74** | *n*-Pr | OEt | Ph | 1 |
| **75** | Me | Me | Ph | 2 |
| **76** | $C_7H_{11}$ | Me | Ph | 1 |

The requisite β-dicarbonyl compound (1 mmol) and CAN (5 mol%) were added to a stirred solution of the primary amine (1 mmol) in ethanol (3

mL). Stirring was continued for 30 min under reflux, at which point the formation of the intermediate β-enaminone was complete (for reference purposes, we isolated enamine **61**, which is described below), after which the requisite unsaturated aldehyde (1 mmol) was added and the mixture was heated at reflux for a further 30 min. After completion of the reaction, as monitored by TLC, the mixture was diluted with dichloromethane (20 mL) and washed with water (5 mL). The organic phase was dried (anhydrous $Na_2SO_4$) and the solvent was removed by rotary evaporation. The residue was purified by flash column chromatography eluting with a petroleum ether/ethyl acetate mixture (85:15, v/v).

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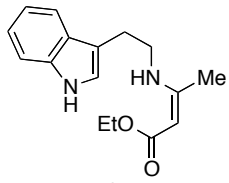
**(*Z*)-Ethyl 3-((2-(1*H*-indol-3-yl)ethyl)amino)but-2-enoate (61):**




**61**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), tryptamine (160 mg, 1 mmol), yield: 266 mg (98 %) as a viscous pale brown oil oil.

Data of **61**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.27 (t, *J* = 7.1Hz, 3H), 1.87 (s, 3H), 3.04 (t, *J* = 7.0 Hz, 2H), 3.48-3.58 (m, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 7.10-7.29 (m, 3H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 8.12 (s, 1H), 8.70 (s, 1H).

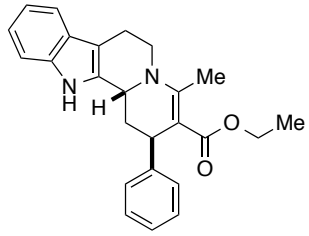
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): 14.7, 19.5, 26.7, 43.6, 58.4, 82.1, 111.4, 112.6, 118.5, 119.5, 122.2, 122.4, 127.2, 136.4, 161.9, 170.7.

**IR** (Neat): 2920, 1655, 1502, 1456, 1407, 1325 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{16}H_{20}N_2O_2$ (M = 272.15): C, 70.56; H, 7.40; N, 10.29; Found: C, 70.43; H, 7.50; N, 10.05.

---

**(±)-(2*S**,12b*S**)-Ethyl 4-methyl-2-phenyl-1,2,6,7,12,12b-hexahydro-indolo[2,3-a]quinolizine-3-carboxylate (62):**




**62**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), tryptamine (160 mg, 1 mmol), cinnamaldehyde (132 mg, 1 mmol), yield: 331 mg (86 %) as a yellow solid.

Data of **62**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 0.80 (t, *J* = 7.1 Hz, 3 H), 1.86 (td, *J* = 12.4, 5.3 Hz, 1H), 2.11 (ddd, *J* = 12.8, 3.5, 2.5 Hz, 1 H), 2.46 (s, 3 H), 2.51–2.74 (m, 2 H), 2.96 (ddd, *J* = 15.0, 10.9, 4.1 Hz, 1H), 3.75 (q, *J* = 7.1 Hz, 2H), 4.06–4.17 (m, 3H), 6.89–6.95 (m, 3H), 7.01–7.15 (m, 5 H), 7.27–7.30 (m, 1 H), 7.58 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 17.9, 22.8, 36.3, 38.5, 45.2, 49.9, 59.3, 97.2, 109.4, 111.3, 118.4, 120.0, 122.1, 126.4, 127.2, 128.2, 128.6, 134.4, 136.4, 147.4, 155.2, 169.4.

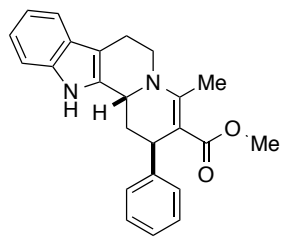
**IR** (NaCl): 3314, 1556, 1454, 1305, 1212, 1095 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{26}N_2O_2$ (M = 386.20): C 77.69, H 6.78, N 7.25; found: C 77.53, H 6.63, N 6.99.

**Mp**: 175–176 °C.

---

**(±)-(2*S**,12b*S**)-Methyl 4-methyl-2-phenyl-1,2,6,7,12,12b-hexahydro-indolo[2,3-*a*]quinolizine-3-carboxylate (63):**




**63**

Prepared from methyl acetoacetate (116 mg, 1 mmol), tryptamine (160 mg, 1 mmol), cinnamaldehyde (132 mg, 1 mmol), yield: 327 mg (88 %) as an orange solid.

Data of **63**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 2.08 (td, *J* = 5.0, 12.5 Hz, 1H), 2.35 (d, *J* = 12.5

Hz, 1H), 2.70 (s, 3H), 2.75-2.95 (m, 2H), 3.14-3.25 (m, 1H), 3.52 (s, 3H), 4.26-4.40 (m, 3H), 7.00-7.17 (m, 2H), 7.20-7.38 (m, 6H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.71 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 17.9, 22.8, 36.4, 38.2, 45.3, 50.0, 51.1, 96.4, 109.4, 111.3, 118.4, 120.0, 122.2, 126.5, 127.2, 128.2, 128.7, 134.4, 136.4, 147.0, 155.4, 169.8.

**IR** (NaCl): 3302, 2921, 1651, 1548, 1428, 1353, 1305, 1223, 1183, 1123, 1098, 1029 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{24}H_{24}N_2O_2$ (M = 372.18): C, 77.39; H, 6.49; N, 7.52. Found: C, 77.44; H, 6.48; N, 7.10 %.

**Mp**: 166-167 °C.

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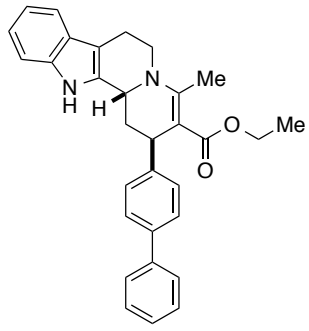
**(±)-(2*S**,12b*S**)-Ethyl 2-([1,1'-biphenyl]-4-yl)-4-methyl-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3-carboxylate (64):**




**64**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), tryptamine (160 mg, 1 mmol), 4-phenyl-cinnamadehyde (208 mg, 1 mmol), yield: 397 mg (86 %) as a yellow solid.

Data of **64**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.05(t, *J* = 7.0 Hz, 3H), 2.11 (td, *J* = 5.2, 12.4 Hz, 1H), 2.39 (dt, *J* = 3.1, 12.8 Hz, 1H), 2.7 (s, 3H), 2.70-2.95 (m, 2H), 3.15-3.26 (td, *J* = 3.8, 13.7 Hz, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 4.34-4.38 (m, 3H), 7.10-7.22 (m, 2H), 7.25-7.41 (m, 4H), 7.43-7.64 (m, 7H), 7.81 (S, 1H);

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ (one aromatic carbon merged) 14.7, 18.0, 22.8, 36.3, 38.2, 45.2, 50.0, 59.4, 97.1, 109.3, 111.3, 118.4, 120.0, 122.1, 127.2, 127.3, 127.4, 128.7, 129.1, 134.4, 136.4, 139.2, 141.4, 146.6, 155.3, 169.5.

**IR** (NaCl) 3301, 2925, 1651, 1551, 1486, 1427, 1352, 1305, 1212, 1111, 1094, 1030 $cm^{-1}$;

**Elemental analysis**: Anal. Calcd for $C_{31}H_{30}N_2O_2$: C, 80.49; H, 6.54; N, 6.06. Found: C, 80,67; H, 6.59; N, 5.96 %.

**Mp**: 143-144 °C.

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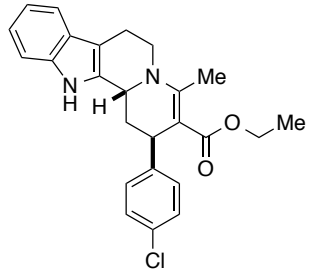
**(±)-(2*S**,12b*S**)-Ethyl 2-(4-chlorophenyl)-4-methyl-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3-carboxylate (65):**




**65**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), tryptamine (160 mg, 1 mmol), 4-chloro-cinnamaldehyde (166 mg, 1 mmol), yield: 369 mg (88 %) as an orange solid.

Data of **65**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.03 (t, *J* = 7.1 Hz, 3 H), 2.09 (td, = 12.3, 5.2 Hz, 1H), 2.30 (dt, *J* = 12.8, 2.5 Hz, 1H), 2.68 (s, 3 H), 2.77–2.96 (m, 2 H), 3.22 (td, *J* = 10.7, 4.1 Hz, 1 H), 3.98 (q, *J* = 7.1 Hz, 2 H), 4.26–4.39 (m, 3 H), 7.09–7.22 (m, 4 H), 7.28–7.32 (m, 3 H), 7.51 (d, *J* = 7.0 Hz, 1 H), 7.72 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.7, 17.9, 22.7, 36.3, 38.0, 45.2, 49.8, 59.4, 96.7, 109.5, 111.3, 118.4, 120.1, 122.3, 127.1, 128.7, 129.6, 132.0, 134.1, 136.4, 146.0, 155.4, 169.2.

**IR** (NaCl): 2923, 1556, 1093 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{25}ClN_2O_2$ (M = 420.16): C, 71.33; H, 5.99; N, 6.66. Found: C, 71.02; H, 5.76; N, 6.32.

**Mp**: 118–119 °C.

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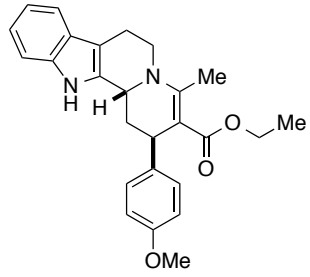
**(±)-(2*S**,12b*S**)-Ethyl 2-(4-methoxyphenyl)-4-methyl-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]qu inolizine-3-carboxylate (66):**




**66**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), tryptamine (160 mg, 1 mmol), 4-methoxycinnamaldehyde (162 mg, 1 mmol), yield: 353 mg (85 %) as an orange solid.

Data of **66**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.04 (t, *J* = 7.1 Hz, 3H), 2.06 (td, *J* = 5.1, 12.4 Hz, 1H), 2.30 (dd, *J* = 2.2, 12.7, Hz, 1H), 2.67 (s, 3H), 2.75-2.96 (m, 2H), 3.21 (td, *J* = 4.1, 10.9 Hz, 1H), 3.82 (s, 3H), 3.98 (q, *J* = 7.1 Hz, 2H), 4.29-4.38 (m, 3H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.12-7.20 (m, 4H), 7.26-7.28 (m, 1H), 7.51 (d, *J* = 6.8, 1H), 7.4 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14, 18, 22, 36, 37, 45, 49, 55, 59, 97, 109, 111, 114, 118, 120, 122, 127, 129, 134, 136, 139, 154, 158, 169.

**Elemental analysis**: Anal. Calcd for $C_{26}H_{28}N_2O_3$ (M = 416.21): C, 74.97; H, 6.78; N, 6.73. Found: C, 74.90; H, 6.66; N, 6.56 %.

**IR** (NaCl) 3296, 2930,1731, 1651, 1607, 1555, 1510, 1455, 353, 1175, 1108, 1094, 1031 $cm^{-1}$.

**Mp**: 116-117 °C.

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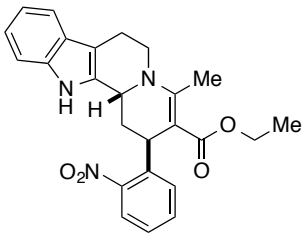
**(±)-(2*S**,12b*S**)-Ethyl 4-methyl-2-(2-nitrophenyl)-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3-carboxylate (67):**




**67**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), tryptamine (160 mg, 1 mmol), 2-nitro-cinnamadehyde (177 mg, 1 mmol), yield: 120 mg (28 %) as a pale brown solid.

Data of **67**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 0.90 (t, *J* = 7.0 Hz, 3H), 2.15–2.29 (m, 1H), 2.54–2.98 (m, 6H), 2.79–2.98 (m, 4H), 3.24–3.34 (m, 1 H), 3.83 (q, *J* = 6.9 Hz, 2 H), 4.41–4.56 (m, 2 H), 4.65 (d, *J* = 3.6 Hz, 1H), 7.10–7.21 (m, 3H), 7.29–7.57 (m, 4H), 7.85 (d, *J* = 7.8 Hz, 1H), 8.02 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14, 17, 22, 34, 34.5, 45, 50, 59, 97, 109, 111, 118, 120, 122, 124, 127, 127.3, 130, 132, 133, 136, 142, 150, 156, 168.

**IR** (NaCl): 3290, 2979, 1731, 1651, 1555, 1434, 1353, 1305, 1216, 1124, 1097, 1031 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{25}N_3O_4$ (M = 431.18): C 69.59, H 5.84, N 9.74; found: C 69.25, H 5.59, N 9.50.

**Mp**: 135–136 °C.

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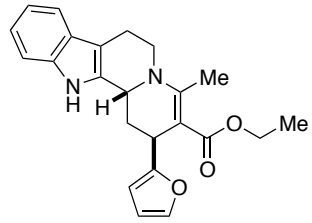
**(±)-(2*S**,12b*S**)-Ethyl 2-(furan-2-yl)-4-methyl-1,2,6,7,12,12b-hexahydro-indolo[2,3-*a*]quinolizine-3-carboxylate (68):**




**68**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), tryptamine (160 mg, 1 mmol), (*E*)-3-(furan-2-yl)propenal (122 mg, 1 mmol), yield: 289 mg (77 %) as a brown solid.

Data of **68**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.16 (t, *J* = 7.1 Hz, 3H), 1.94 (td, *J* = 4.9, 12.4 Hz, 1H), 2.55-2.62 (m, 4H), 2.75-2.96 (m, 2H), 3.18 (ddd, *J* = 6.2, 10.3, 13.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.28-4.36 (m, 3H), 6.0 (d, *J* = 3.1 Hz, 1H), 6.31 (dd, *J* = 1.8, 3.1 Hz, 1H), 7.11-7.23 (m, 2H), 7.29-7.39 (m, 2H), 7.50-7.53 (d, *J* = 7.1 Hz, 1H), 7.80 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.8, 18.0, 22.7, 32.7, 32.9, 45.1, 50.8, 59.4, 95.7, 106.8, 109.4, 110.6, 111.3, 118.4, 120.0, 122.2, 127.2, 134.3, 136.5, 141.4, 155.2, 159.5, 169.3.

**IR** (NaCl): 2924, 1555, 1454, 1217, 1120, 1095 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{23}H_{24}N_2O_3$ (M = 376.18): C, 73.38; H, 6.43; N, 7.44. Found: C, 73.09; H, 6.31; N, 7.22 %.

**Mp**: 125-126 °C.

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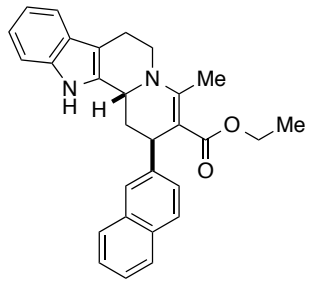
**(±)-(2*S**,12b*S**)-Ethyl 4-methyl-2-(naphthalen-1-yl)-1,2,6,7,12,12b-hexahydroindolo[2, 3-*a*]quinolizine-3-carboxylate (69):**




**69**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), tryptamine (160 mg, 1 mmol), (*E*)-3-(naphthalen-2-yl)acrylaldehyde (182 mg, 1 mmol), yield: 401 mg (92 %) as an orange solid.

Data of **69**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 0.82 (t, *J* = 7.1 Hz, 3H), 2.20 (ddd, *J* = 15.7, 12.3, 5.7 Hz, 1H), 2.42 (ddd, *J* = 12.5, 3.2, 1.9 Hz, 1H), 2.75 (s, 3H), 2.83-2.99 (m, 2H), 3.25 (ddd, *J* = 14.8, 10.8, 4.3 Hz, 1H), 3.90 (q, *J* = 7.0 Hz, 2H), 4.29-4.43 (m, 2H), 5.19 (d, *J* = 5.0 Hz, 1H), 7.10-7.23 (m, 3H), 7.32-7.68 (m, 6H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 18.1, 22.8, 34.4, 34.7, 45.0, 50.3, 59.2, 97.7, 109.5, 111.2, 118.3, 120.0, 122.1, 123.4, 125.7, 125.8, 126.1, 126.4, 127.1, 127.2, 129.5, 131.3, 134.2, 134.6, 136.3, 142.7, 155.5, 169.4.

**IR** (NaCl): 2925, 1556, 1219, 1098 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{29}H_{28}N_2O_2$ (M = 436.22): C, 79.79; H, 6.46; N, 6.42;. Found: C, 79.76; H, 6.39; N, 6.27 %.

**Mp**: 267-268 °C.

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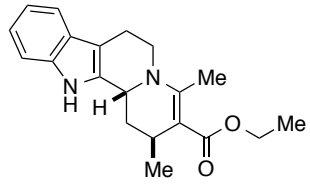
**(±)-(2*S**,12b*S**)-Ethyl 2,4-dimethyl-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3-carboxylate (70):**



**70**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), tryptamine (160 mg, 1 mmol), methacrylaldehyde (70 mg, 1 mmol), yield: 200 mg (62 %) as a brown solid.

Data of **70**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.20 (d, *J* = 6.8 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.84 (td, *J* = 5.0, 12.4 Hz, 1H), 2.09 (ddd, *J* = 2.3, 3.9, 12.8 Hz, 1H), 2.51 (s, 3H), 2.75-2.95 (m, 2H), 3.10-3.26 (m, 2H), 4.09-4.31 (m, 3H), 4.57 (td, *J* = 2.0, 12.2 Hz, 1H), 7.11-7.23 (m, 2H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.53 (d, *J* = 7.0 Hz, 1H), 7.84 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 13.1, 16.2, 20.7, 20.9, 25.0, 33.2, 43.4, 48.2, 57.5, 99.4, 107.5, 109.5, 116.6, 118.2, 120.3, 125.4, 133.1, 134.6, 151.6, 168.0;

**IR** (NaCl): 3310, 2975, 2359, 1731, 1651, 1555, 1454, 1305, 1226, 1130, 1091, 1040 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.41; H, 7.25; N, 6.87 %.

**Mp**: 108-109 °C.

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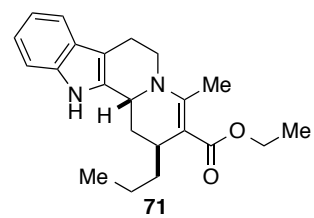
**(±)-(2*S**,12b*S**)-Ethyl 4-methyl-2-propyl-1,2,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizine-3-carboxylate (71):**



**71**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), tryptamine (160 mg, 1 mmol), (*E*)-hex-2-enal (98 mg, 1 mmol), yield: 140 mg (40 %) as an orange solid.

Data of **71**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 0.99 (t, *J* = 6.6 Hz, 3H), 1.28-1.79 (m, 8H), 2.25-2.29 (m, 1H), 2.51 (s, 3H), 2.75-2.99 (m, 3H), 3.20 (td, *J* = 4.4, 11.1 Hz, 1H), 4.08-4.31 (m, 3H), 4.55 (d, *J* = 11.5 Hz, 1H), 7.11-7.23 (m, 2H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.1 Hz, 1H), 7.91 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 14.9, 17.9, 20.7, 22.8, 31.3, 31.7, 38.5, 45.3, 50.3, 59.3, 100.7, 109.3, 111.3, 118.4, 120.0. 122.2, 127.3, 135.0, 136.4, 153.0, 169.9.

**IR** (NaCl): 3300, 2928, 1644, 1548, 1454, 1305, 1222, 1097 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{22}H_{28}N_2O_2$: , 74.97; H, 8.01; N, 7.95. Found: C, 74.44; H, 7.85; N, 7.66 %.

**Mp**: 97-98 °C.

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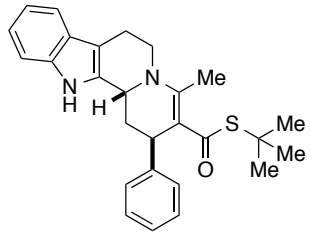
**(±)-(2*S**,12b*S**)-*S*-*tert*-butyl-4-methyl-2-phenyl-1,2,6,7,12,12b-hexahydro-indolo[2,3-*a*]quinolizine-3-carbothioate (72):**




**72**

Prepared from *S*-tert-butyl 3-oxobutanethioate (174 mg, 1 mmol), tryptamine (160 mg, 1 mmol), cinnamaldehyde (132 mg, 1 mmol), yield: 301 mg (70 %) as a yellow solid.

Data of **72**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.40 (s, 9H), 2.11 (td, *J* = 4.7, 12.5 Hz, 1H), 2.37-2.42 (m, 1H), 2.60 (s, 3H), 2.75-2.93 (m, 2H), 3.18 (td, *J* = 3.8, 13.5, Hz, 1H), 4.21-4.44 (m, 3H), 7.09-7.20 (m, 2H), 7.27-7.40 (m, 6H), 7.50 (d, *J* = 7.0 Hz, 1H), 7.67 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 18.5, 22.7, 30.6, 36.6, 39.1, 45.4, 47.1, 50.1, 106.4, 109.5, 111.3, 118.4, 120.1, 122.3, 126.6, 127.1, 128.4, 128.8, 134.0, 136.4, 145.8, 153.1, 192.1;

**IR** (NaCl): 3310, 2923, 1614, 1519, 1453, 1350, 1304, 1161, 1054 $cm^{-1}$;

**Elemental analysis**: Anal. Calcd for $C_{27}H_{30}N_2OS$ (M = 430.21): C, 75.31; H, 7.02; N, 6.51; S, 7.45. Found: C, 75.10; H, 7.02; N, 6.47; S, 7.49 %.

**Mp**: 139-140 °C.

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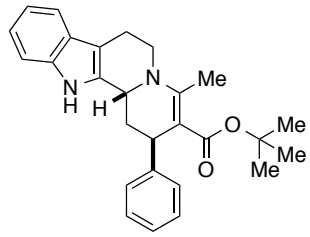
**(±)-(2*S**,12b*S**)-*tert*-Butyl 4-methyl-2-phenyl-1,2,6,7,12,12b-hexahydro-indolo[2,3-*a*]quinolizine-3-carboxylate (73):**




**73**

Prepared from *tert*-butyl acetoacetate (158 mg, 1 mmol), tryptamine (160 mg, 1 mmol), cinnamaldehyde (132 mg, 1 mmol), yield: 281 mg (68 %) as a brown solid.

Data of **73**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.21 (s, 9H), 2.11 (td, *J* = 5.4, 11.7 Hz, 1H), 2.27 (d, *J* = 12.6 Hz, 1H), 2.63 (s, 3H), 2.76-2.94 (m, 2H), 3.22 (td, *J* = 3.5, 13.3 Hz, 1H), 4.28 (m, 3H), 7.09-7.19 (m, 2H), 7.24-7.37 (m, 6H), 7.51 (d, *J* = 6.6 Hz, 1H), 7.63 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 18.0, 22.8, 28.5, 36.6, 39.3, 44.9, 49.6, 78.6, 99.7, 109.5, 111.2, 118.4, 120.0, 122.1, 126.3, 127.2, 128.4, 128.5, 134.4, 136.4, 148.1, 154.5, 169.0;

**IR** (NaCl): 3310, 2924, 2359, 1651, 1556, 1491, 1453, 1389, 1365, 1304, 1226, 1171, 1125, 1094, 1030 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{30}N_2O_2$ (M = 414.23): C, 78.23; H, 7.29; N, 6.76; Found: C, 78.11; H, 7.22; N, 6.91 %.

**Mp**: 236-237 °C.

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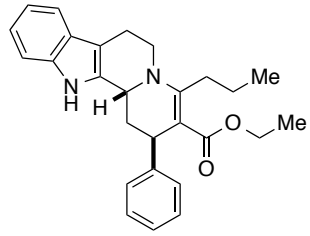
**(±)-(2*S**,12b*S**)-Ethyl 2-phenyl-4-propyl-1,2,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizine-3-carboxylate (74):**



**74**

Prepared from ethyl 3-oxohexanoate (158 mg, 1 mmol), tryptamine (160 mg, 1 mmol), cinnamaldehyde (132 mg, 1 mmol), yield: 207 mg (50 %) as an orange solid.

Data of **74**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.00-1.18 (m, 6H), 1.69-1.74 (m, 1H), 1.83-1.92 (m, 1H), 2.09 (td, *J* = 12.3, 5.2 Hz, 1H), 2.29-2.34 (m, 1H), 2.79-2.91 (m, 3H), 3.25 (td, *J* = 10.4, 3.7 Hz, 1H), 3.44 (td, *J* = 11.4, 5.1 Hz, 1H), 3.97 (q, *J* = 7.0 Hz, 2H), 4.28-4.34 (m, 3H), 7.10-7.37 (m, 8H), 7.51 (d, *J* = 6.6 Hz, 1H), 7.69 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.7, 14.8, 22.9, 23.1, 32.1, 36.4, 38.3, 44.9, 49.8, 59.2, 96.2, 109.3, 111.3, 118.4, 120.0, 122.1, 126.3, 127.1, 128.2, 128.6, 134.5, 136.4, 147.6, 159.4, 168.9.

**IR** (NaCl): 3306, 2960, 1651, 1547, 1454, 1353, 1304, 1206, 1123, 1096, 1034 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{30}N_2O_2$ (M = 414.23) C, 78.23; H, 7.29; N, 6.76. Found: C, 78.09; H, 7.19; N, 6.59 %.

**Mp**: 165-166 °C.

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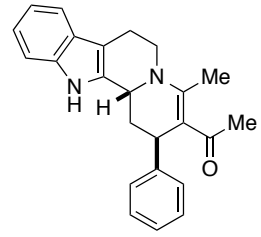
**(±)-(2*S**,12b*S**)-4-Methyl-2-phenyl-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-3-yl)ethanone (75):**



**75**

Prepared from acetylacetone (100 mg, 1 mmol), tryptamine (160 mg, 1 mmol), cinnamaldehyde (132 mg, 1 mmol), yield: 284 mg (80 %) as an orange solid.

Data of **75**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 2.02 (s, 3H), 2.13 (td, *J* = 12.5, 4.8 Hz, 1H), 2.45 (dt, *J* = 12.5, 3.4 Hz, 1H), 2.72 (s, 3H), 2.75-2.97 (m, 2H), 3.20 (td, *J* = 11.2, 4.4 Hz, 1H), 4.18 (s, 1H), 4.29 (dd, *J* = 12, 1.6 Hz, 1H), 4.41 (dd, *J* = 13.1, 2.0, 1H), 7.09-7.20 (m, 3H), 7.25-7.28 (m, 3H), 7.34-7.40 (m, 2H), 7.49-7.52 (m, 1H), 8.00 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 18.5, 22.7, 29.9, 36.6, 40.0, 45.5, 50.3, 106.4, 109.2, 111.4, 118.4, 119.9, 122.1, 126.9, 127.0, 128.4, 129.0, 134.2, 136.5, 146.0, 156.3, 197.4.

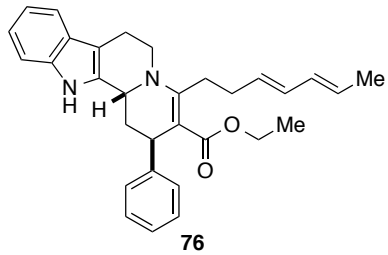
**IR** (NaCl) 2925, 1505, 1454 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{24}H_{24}N_2O$ (M = 356.19): C, 80.87; H, 6.79; N, 7.86. Found: C, 80.75; H, 6.93; N, 7.63 %.

**Mp**: 115-116 °C.

---

**(±)-(2*S**,12b*S**)-Ethyl 4-[(3*E*,5*E*)-hepta-3,5-dien-1-yl]-2-phenyl-1,2,6,7,12, 12b-hexahydroindolo[2,3-*a*]quinolizine-3-carboxylate (76):**




**76**

Prepared from (6*E*,8*E*)-ethyl 3-oxodeca-6,8-dienoate[142] (210 mg, 1 mmol), tryptamine (160 mg, 1 mmol), cinnamaldehyde (132 mg, 1 mmol), yield: 209 mg (45 %) as a brown solid.

Data of **76**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.14 (t, *J* = 7.1 Hz, 3H), 1.90 (d, *J* = 6.8 Hz, 3H), 2.19 (td, *J* = 12.3, 5.1 Hz, 1H), 2.42 (dt, *J* = 12.6, 3.2 Hz, 1H), 2.53-2.60 (m, 1H), 2.67-2.84 (m, 1H), 2.90-3.01 (m, 3H), 3.36 (td, *J* = 14.0, 4.1 Hz, 1H), 3.7 (td, *J* = 13.0, 5.3 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 4.36-4.45 (m, 3H), 5.73-

142 Hiyama, T.; Morizawa, Y.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, 54, 2151.

5.94 (m, 2H), 6.15-6.35 (m, 2H), 7.21-7.32 (m, 2H), 7.36-7.48 (m, 6H), 7.60-7.64 (m, 1H), 7.80 (s, 1H).

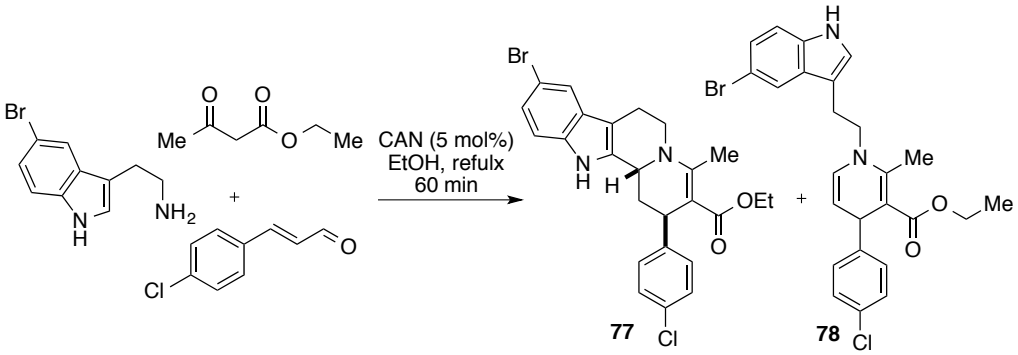
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 18.5, 23.1, 29.9, 32.4, 36.4, 38.3, 44.9, 49.8, 59.3, 96.7, 109.4, 111.2, 118.4, 120.0, 122.2, 126.3, 127.1, 127.9, 128.2, 128.7, 130.9, 131.2, 131.9, 134.3, 136.4, 147.5, 158.5, 168.7.

**IR** (NaCl): 2930, 1735, 1698, 1622, 1526, 1244, 1192, 1117, 1085 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{31}H_{34}N_2O_2$ (M = 466.26): C, 79.79; H, 7.34; N, 6.00. Found: C, 79.55; H, 7.23; N, 5.90 %.

**MP**: 178-179°C.

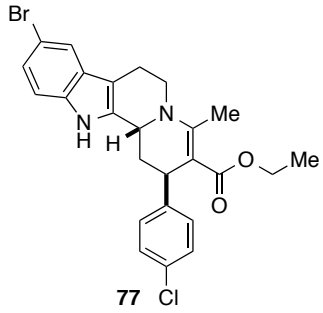
### 7.4.2. Synthesis of compounds 77 and 78




Ethyl acetoacetate (130 mg, 1 mmol) and CAN (5 mol%) were added to a stirred solution of bromotryptamine[143] (238 mg, 1 mmol) in ethanol (3 mL). Stirring was continued for 30 min under reflux, after which 4-chlorocinnamaldehyde (166 mg, 1 mmol) was added and the mixture was heated at reflux for a further 30 min. After completion of the reaction, as monitored by TLC, the mixture was diluted with minimum dichloromethane (20 mL) and washed with water (5 mL). The organic phase was dried (anhydrous $Na_2SO_4$) and the solvent was removed on rotavapor. The residue was purified by flash column chromatography eluting with a petroleum ether/ethyl acetate mixture to give compounds **77** (199 mg, 40%) and **79** (134 mg, 27%). Characterization data for both compounds follow.

143 Synthesis of 5-bromotryptamine: Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796.

**(±)-(2*S**,12b*S**)-Ethyl 9-bromo-2-(4-chlorophenyl)-4-methyl-1,2,6,7,12, 12b-hexahydroindolo[2,3-*a*]quinolizine-3-carboxylate (77):**




**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.04 (t, *J* = 7.1 Hz, 3H), 2.10 (td, *J* = 12.2, 5.1 Hz, 1H), 2.24-2.33 (m, 1H), 2.68 (s, 3H), 2.77-2.91 (m, 2H), 3.21 (td, *J* = 11.8, 5.2 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 4.24-4.39 (m, 3H), 7.14-7.32 (m, 6H), 7.63 (s, 1H), 7.75 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.7, 17.9, 22.6, 36.2, 38.0, 45.1, 49.7, 59.5, 97.1. 109.3, 112.7, 113.3, 121.2, 125.0, 128.8, 128.9, 129.5, 132.1, 135.0, 135.4, 145.8, 155.3, 169.1.

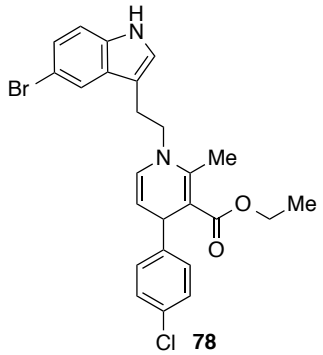
**IR** (NaCl): 2951, 2917, 2846, 1729, 1644, 1551, 1431, 1308, 1217, 1224, 1093, 1027 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{24}BrClN_2O_2$ (M = 498.07): C, 60.07; H, 4.84; N, 5.60. Found: C, 59.87; H, 4.70; N, 5.42 %.

**Mp**: 92-93 °C.

---

**(±)-Ethyl 1-(2-(5-bromo-1*H*-indol-3-yl)ethyl)-4-(4-chlorophenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (78):**




**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.13 (t, *J* = 7.0 Hz, 3H), 2.43 (s, 3H), 3.00 (t, *J* = 7.3 Hz, 2H), 3.59 (quint., *J* = 7.4 Hz, 1H), 3.78 (quint, *J* = 7.4 Hz, 1H), 4.00 (q, *J* = 7.0 Hz, 2H), 4.60 (d, *J* = 5.5 Hz, 1H), 4.90 (dd, *J* = 7.6, 5.5 Hz, 1H), 5.89 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 7.15-7.31 (m, 6H), 7.71 (d, *J* = 1.5 Hz, 1H), 8.16 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 16.1, 26.4, 40.0, 50.9, 59.7, 99.9, 107.9,

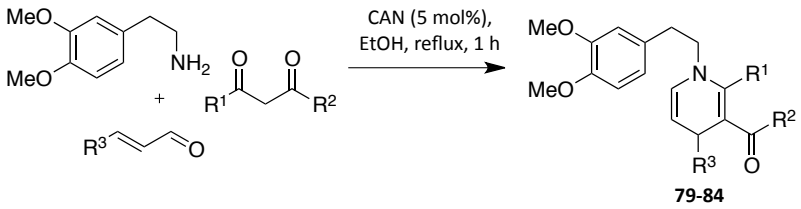
112.2, 113.2, 113.3, 121.4, 123.9, 125.6, 128.6, 129.1, 129.2, 129.3, 135.2, 147.9, 149.1, 150.1, 169.2.

**IR** (NaCl): 2927, 1728, 1651, 1462, 1366, 1269, 1220, 1170, 1092 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{24}BrClN_2O_2$ (M = 498.07): C, 60.07; H, 4.84; N, 5.60. Found: C, 59.21; H, 4.79; N, 5.57 %.

**Mp**: 132-133 °C.

### 7.4.3: General procedure for the synthesis of 2,3,4-substituted dihydropyridine derivatives 79-84.

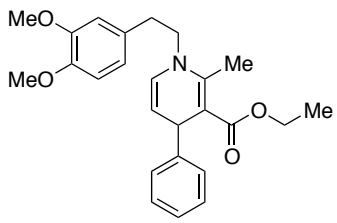



**79-84**

| Cmpd. | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **79** | Me | OEt | Ph |
| **80** | Me | O-$^t$Bu | Ph |
| **81** | Me | OEt | 4-$ClC_6H_4$ |
| **82** | Me | OEt | 4-$MeOC_6H_4$ |
| **83** | Me | OEt | Me |
| **84** | *n*-Pr | OEt | Ph |

2-(3,4-Dimethoxyphenyl)ethylamine (1 mmol) was dissolved in ethanol (3 mL), and the suitable β-ketoester (1 mmol) and CAN (5 mol%) were added. The reaction mixture was refluxed for 30 min, and after enamine formation the suitable aldehyde (1 mmol) was added and reflux was continued for further 30 min. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled and diluted with dichloromethane (20 mL). After washing with water (5 mL), the organic layer was separated and dried over sodium sulphate and solvents were evaporated under reduced pressure. Purification of the crude by chromatography on silica gel (petroleum ether-ethyl acetate 85:15, v/v) as eluent gave the dihydropyridine derivatives.

**(±)-Ethyl 1-(3,4-dimethoxyphenethyl)-2-methyl-4-phenyl-1,4-dihydro-pyridine-3-carboxylate (79):**




**79**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), 3,4-dimethoxyphenethylamine (181 mg, 1 mmol), cinnamaldehyde (132 mg, 1 mmol), yield: 284 mg (70 %) as a brown viscous liquid.

Data of **79**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.11 (t, *J* = 7.1 Hz, 3H), 2.45 (s, 3H), 2.85 (t, *J* = 7.6 Hz, 2H), 3.51 (quint., *J* = 7.7 Hz, 1H), 3.71 (quint., *J* = 7.6 Hz, 1H), 3.07-3.09 (m, 6H), 4.00 (q, *J* = 7.1 Hz, 2H), 4.61 (d, *J* = 5.4 Hz, 1H), 4.96 (dd, *J* = 7.6, 5.4 Hz, 1H), 5.90 (d, *J* = 7.6 Hz, 1H), 6.71-6.85 (m, 3H), 7.17-7.32 (m, 5H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 13.1, 14.6, 35.2, 39.2, 50.9, 54.8, 58.2, 98.9, 107.0, 110.3, 110.9, 119.7, 124.9, 126.3, 127.1. 127.4, 129.5, 146.8, 147.3, 147.8, 147.9, 168.0.

**IR** (NaCl): 2935, 1681, 1621, 1516, 1453, 1418, 1368, 1263, 1238, 1157, 1097, 1028 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{29}NO_4$ (M = 407.21): C, 73.68; H, 7.17; N, 3.44. Found: C, 73.49; H, 7.03; N, 3.29 %.

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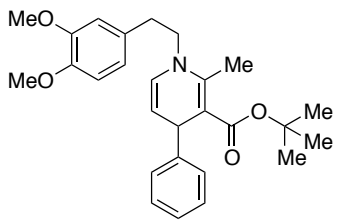
**(±)-*tert*-Butyl 1-(3,4-dimethoxyphenethyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (80):**




**80**

Prepared from *tert*-butyl acetoacetate (158 mg, 1 mmol), 3,4-dimethoxyphenethylamine (181 mg, 1 mmol), cinnamaldehyde (132 mg, 1 mmol), yield: 313 mg (72 %) as a pale brown

viscous oil.

Data of **80**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.27 (s, 9H), 2.42 (s, 3H), 2.84 (t, *J* = 7.5 Hz, 2H), 3.49 (quint, *J* = 7.6 Hz, 1H), 3.67 (quint, *J* = 7.6 Hz, 1H), 3.87-3.90 (m, 6H), 4.59 (d, *J* = 5.0 Hz, 1H), 4.90 (dd, *J* = 7.6, 5.1 Hz, 1H), 5.84 (d, *J* = 7.7 Hz, 1H), 6.72-6.86 (m, 3H), 7.18-7.33 (m, 5H).

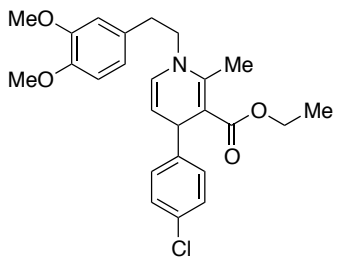
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 16.0, 28.5, 36.7, 41.4, 52.3, 56.3, 79.2, 102.1, 108.2, 111.7, 112.4, 121.1, 126.2, 127.8, 128.5, 128.7, 131.1, 147.5, 148.2, 149.4, 149.7, 169.0.

**IR** (NaCl): 2932, 1714, 1681, 1651, 1591, 1516, 1454, 1418, 1392, 1368, 1263, 1157, 1029 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{33}NO_4$ (M = 435.24): C, 74.45; H, 7.64; N, 3.22. Found: C, 74.30; H, 7.52; N, 3.06 %.

---

**(±)-Ethyl 4-(4-chlorophenyl)-1-(3,4-dimethoxyphenethyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (81):**




**81**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), 3,4-dimethoxyphenethylamine (181 mg, 1 mmol), 4-chlorocinnamaldehyde (166 mg, 1 mmol), yield: 281 mg (68 %) as a beige solid.

Data of **81**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.13 (t, *J* = 7.1 Hz, 3H), 2.46 (s, 3H), 2.85 (t, *J* = 7.5 Hz, 2H), 3.53 (quint., *J* = 7.6 Hz, 1H), 3.71 (quint., *J* = 7.5 Hz, 1H), 3.89-3.90 (m, 6H), 4.01 (q, *J* = 7.0 Hz, 2H), 4.60 (d, *J* = 5.3 Hz, 1H), 4.91 (dd, *J* = 7.5, 5.4 Hz, 1H), 5.90 (d, *J* = 7.6 Hz, 1H), 6.71-6.77 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.24-7.29 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 16.1, 36.6, 40.1, 52.3, 56.3, 59.7, 100.0, 108.0, 111.7, 112.3, 121.2, 128.6, 129.1, 130.7, 131.9, 147.9, 148.3, 149.0, 149.4, 169.2 (one quaternary carbon was merged with others).

**IR** (NaCl): 2932, 1731, 1592, 1516, 1489, 1464, 1367, 1263, 1238, 1158, 1090, 1028 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{28}ClNO_4$ (M = 441.17): C, 67.94; H, 6.39; N, 3.17. Found: C, 67.73; H, 6.28; N, 3.07 %.

**Mp**: 107-108 °C.

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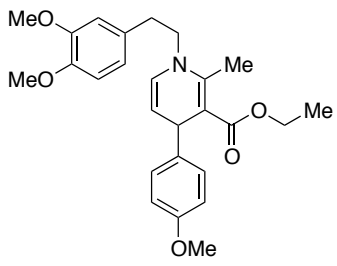
**(±)-Ethyl 1-(3,4-dimethoxyphenethyl)-4-(4-methoxyphenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate (82):**



**82**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), 3,4-dimethoxyphenethylamine (181 mg, 1 mmol), 4-methoxycinnamaldehyde (162 mg, 1 mmol), yield: 284 mg (65 %) as a pale brown paste.

Data of **82**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.15 (t, *J* = 7.1 Hz, 3H), 2.44 (s, 3H), 2.86 (t, *J* = 7.6 Hz, 2H), 3.52 (quint, *J* = 7.5 Hz, 1H), 3.70 (quint, *J* = 7.6 Hz, 1H), 3.80 (s, 3H), 3.87-3.90 (m, 6H), 4.01 (q, *J* = 7.1 Hz, 2H), 4.56 (d, *J* = 5.5 Hz, 1H), 4.95 (dd, *J* = 7.6, 5.5 Hz, 1H), 5.91 (d, *J* = 7.6 Hz, 1H), 6.72-6.86 (m, 5H), 7.15-7.19 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 16.1, 36.6, 39.6, 52.3, 55.6, 56.3, 59.6, 100.8, 108.6, 111.7, 112.3, 113.9 121.1, 128.7, 128.8, 130.9, 141.9, 148.2, 148.3, 149.4, 158.2, 169.5.

**IR** (NaCl): 2933, 2837, 1681, 1651, 1606, 1556, 1514, 1463, 1417, 1368, 1261, 1177, 1157, 1097, 1028 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{26}H_{31}NO_5$ (M = 437.22): C, 71.37; H, 7.14; N, 3.20. Found: C, 71.30; H, 7.09; N, 3.05 %.

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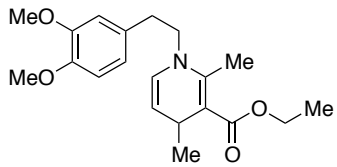
**(±)-Ethyl 1-(3,4-dimethoxyphenethyl)-2,4-dimethyl-1,4-dihydropyridine-3-carboxylate (83):**




**83**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), 3,4-dimethoxyphenethylamine (181 mg, 1 mmol), crotonaldehyde (70 mg, 1 mmol), yield: 213 mg (62 %) as a brown solid.

Data of **83**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.33 (s, 3H), 2.78 (t, *J* = 7.4 Hz, 2H), 3.34-3.48 (m, 2H), 3.67 (quint, *J* = 7.3 Hz, 1H), 3.88-3.89 (m, 6H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.87 (dd, *J* = 7.5, 5.8 Hz, 1H), 5.79 (d, *J* = 7.5 Hz, 1H), 6.69-6.84 (m 3H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.8, 16.0, 25.3, 28.6, 36.6, 52.1, 56.2, 59.5, 101.5, 109.4, 111.7, 112.4, 121.1, 129.2, 131.1, 148.1, 148.7, 149.3, 169.6.

**IR** (NaCl) 2954, 1681, 1591, 1556, 1516, 1464, 1454, 1416, 1395, 1359, 1335, 1263, 1237, 1169, 1141, 1099, 1029 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{20}H_{27}NO_4$ (M = 345.19): C, 69.54; H, 7.88; N, 4.05. Found: C, 68.12; H, 7.59; N, 4.15 %.

**Mp**: 79-80 °C.

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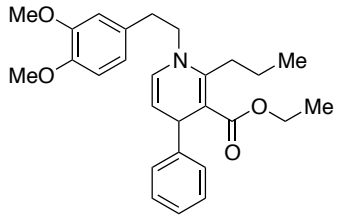
**(±)-Ethyl 1-(3,4-dimethoxyphenethyl)-4-phenyl-2-propyl-1,4-dihydro-pyridine-3-carboxylate (84):**




**84**

Prepared from ethyl 3-oxohexanoate (158 mg, 1 mmol), 3,4-dimethoxyphenethylamine (181 mg, 1 mmol), cinnamaldehyde (132 mg, 1 mmol), yield: 261 mg (60 %) as an orange paste.

Data of **84**:

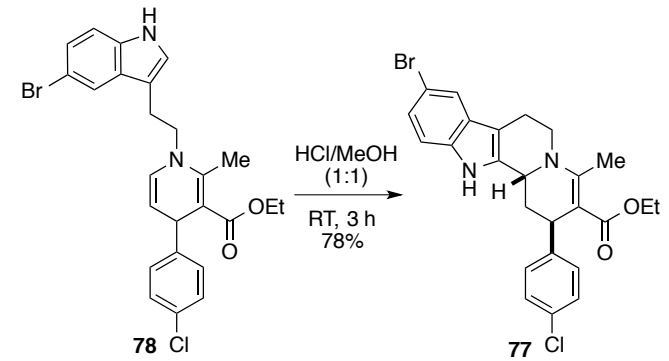
**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.02-1.15 (m, 6H), 1.59-1.69 (m, 2H), 2.81-2.90 (m, 4H), 3.46 (quint., *J* = 7.0 Hz, 1H), 3.66 (quint., *J* = 7.1 Hz, 1H), 3.87-3.90 (m, 6H), 4.01 (q, *J* = 7.0 Hz, 2H), 4.62 (d, *J* = 5.5 Hz, 1H), 4.99 (dd, *J* = 7.6, 5.6 Hz, 1H), 5.91 (d, *J* = 7.6 Hz, 1H), 6.72-6.86 (m, 3H), 7.16-7.29 (m, 5H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 14.7, 22.9, 30.7, 37.0, 40.5, 52.1, 56.2, 56.3, 59.5, 99.7, 108.7, 111.8, 112.3, 121.0, 126.3, 127.7, 128.6, 128.9, 130.9, 148.2, 149.4, 149.5, 152.9, 168.8.

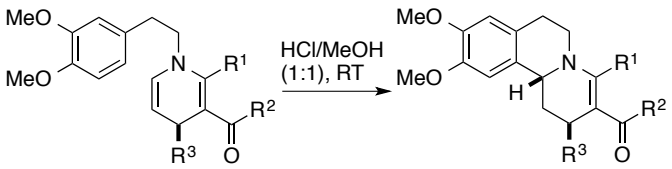
**IR** (NaCl): 2961, 2934, 2872, 1682, 1591, 1516, 1454, 1418, 1367, 1263, 1238, 1158, 1101, 1029 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{33}NO_4$ (M = 435.24): C, 74.45; H, 7.64; N, 3.22. Found: C, 74.25; H, 7.51; N, 3.02 %.

### 7.4.4: General procedure for the cyclisation of compounds 78-84 to arenoquinolizines 77, 85-90.




**78** **77**




**79-84** **85-90**

| Cmpd. | $R^1$ | $R^2$ | $R^3$ | Time, h |
|---|---|---|---|---|
| **85** | Me | OEt | Ph | 2 |
| **87** | Me | OEt | 4-$ClC_6H_4$ | 2 |
| **88** | Me | OEt | 4-$MeOC_6H_4$ | 4 |
| **89** | Me | OEt | Me | 8 |
| **90** | *n*-Pr | OEt | Ph | 2 |

The requisite starting material (**78**-**84**) (0.5 mmol) was added to a stirred solution of aqueous HCl (37 %)/MeOH (1:1, 2 mL). Stirring was continued at room temperature for the times specified in the table below, with completion of the reactions being monitored by TLC. Dichloromethane (20 mL) was added to the reaction mixture, and the resulting mixture was washed with water (5 mL). The organic layer was dried over anhydrous $Na_2SO_4$ and the solvent was evaporated under reduced pressure.

Purification of the residue by chromatography on silica gel, eluting with petroleum ether/EtOAc (gradient from 85:15-90:10), gave the expected compounds.

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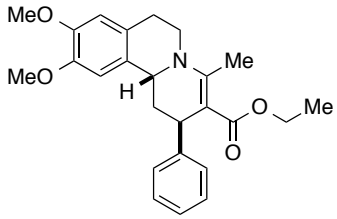
**(±)-(2*S**,11b*S**)-Ethyl 9,10-dimethoxy-4-methyl-2-phenyl-2,6,7,11b-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (85):**




**85**

Prepared from compound 79 (203 mg, 0.5 mmol), yield: 152 mg (75 %) as a brown paste.

Data of **85**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.11 (t, *J* = 7.0 Hz, 3H), 2.10 (td, *J* = 12.6, 5.3 Hz, 1H), 2.48 (dt, *J* = 12.9, 2.6 Hz, 1H), 2.77-2.82 (m, 4H), 3.04 (td, *J* = 15.2, 3.7 Hz, 1H), 3.28 (td, *J* = 13.8, 2.6 Hz, 1H), 3.91-4.12 (m, 8H), 4.26-4.38 (m, 3H), 6.54 (s, 1H), 6.72 (s, 1H), 7.28-7.48 (m, 5H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 17.7, 30.2, 38.5, 39.1, 44.5, 52.4, 56.2, 56.5, 59.1, 97.1, 109.2, 111.5, 126.1, 127.5, 128.3, 128.5, 129.9, 147.8, 147.9, 148.0, 154.9, 169.5.

**IR** (NaCl): 2931, 2836, 1728, 1673, 1563, 1513, 1433, 1362, 1290, 1215, 1120, 1090 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{29}NO_4$ (M = 407.21): C, 73.68; H, 7.17; N, 3.44. Found: C, 73.59; H, 7.31; N, 4.19 %.

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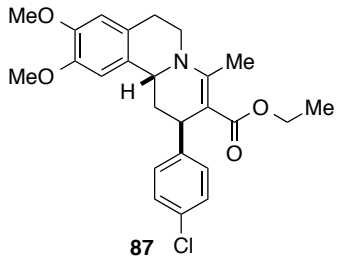
**(±)-(2*S**,11b*S**)-Ethyl 2-(4-chlorophenyl)-9,10-dimethoxy-4-methyl-2,6,7, 11b-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (87):**




Prepared from compound 81 (220.5 mg, 0.5 mmol), yield: 167 mg (76 %) as a brown paste.

Data of **87**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.01 (t, *J* = 7.0 Hz, 3H), 1.97 (td, *J* = 12.8, 5.4 Hz, 1H), 2.27 (dt, *J* = 13.0, 3.1 Hz, 1H), 2.64-2.71 (m, 4H), 2.92 (td, *J* = 15.2, 3.8 Hz, 1H), 3.16 (td, *J* = 11.4, 3.0 Hz, 1H), 3.81 (s, 3H), 3.87 (s, 3H), 3.96 (q, *J* = 7.0 Hz, 2H), 4.09-4.23 (m, 3H), 6.39 (s, 1H), 6.61 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.28-7.32 (m, 2H).

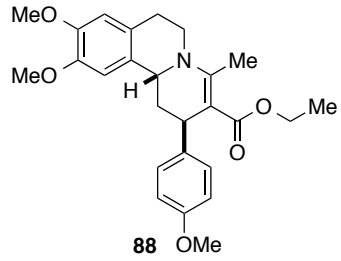
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 17.7, 30.1, 38.5, 38.7, 44.4, 52.3, 56.2, 56.5, 59.2, 96.7, 109.2, 111.5, 127.5, 128.6, 129.6, 129.7, 131.7, 146.7, 147.9, 148.0, 155.2, 169.3.

**IR** (NaCl): 2930, 1672, 1557, 1513, 1488, 1433, 1362, 1256, 1215, 1121, 1089 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{28}ClNO_4$: C, 67.94; H, 6.39; N, 3.17. Found: C, 67.77; H, 6.15; N, 2.97 %.

---

**(±)-(2*S**,11b*S**)-Ethyl 9,10-dimethoxy-2-(4-methoxyphenyl)-4-methyl-2,6, 7,11b-tetrahy dro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (88):**




Prepared from compound 82 (218.5 mg, 0.5 mmol), yield: 167 mg (77 %) as a brown solid.

Data of **88**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.03 (t, *J* = 7.0 Hz, 3H), 1.95 (td, *J* = 12.6, 5.3 Hz, 1H), 2.29-2.35 (m, 1H), 2.64-2.71 (m, 4H), 2.93 (td, *J* = 14.4, 3.1 Hz, 1H), 3.16 (td, *J* = 13.7,

2.5 Hz, 1H), 3.77-3.87 (m, 9H), 3.98 (q, *J* = 7.0 Hz, 2H), 4.14-4.20 (m, 3H), 6.43 (s, 1H), 6.61 (s, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.7, 17.7, 30.2, 38.3, 38.7, 44.4, 52.4, 55.6, 56.2, 56.5, 59.2, 97.6, 109.2, 111.5, 113.8, 127.5, 129.2, 130.0, 140.1, 147.8, 147.9, 154.7, 158.0, 169.6.

**IR** (NaCl): 2929, 1727, 1671, 1607, 1563, 1511, 1463, 1362, 1292, 1250, 1215, 1120, 1034 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.19; H, 7.06; N, 3.02 %.

**Mp**: 82-83 °C.

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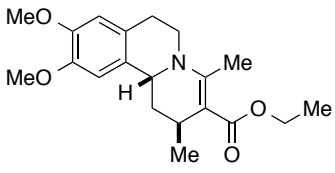
**(±)-(2*R**,11b*S**)-Ethyl 9,10-dimethoxy-2,4-dimethyl-2,6,7,11b-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (89):**




**89**

Prepared from compound 83 (172.5 mg, 0.5 mmol), yield: 132 mg (77 %) as a brown solid.

Data of **89**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.19 (d, *J* = 6.7 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.70 (td, *J* = 12.3, 5.2 Hz, 1H), 2.07 (ddd, *J* = 13.0, 5.4, 2.0 Hz, 1H), 2.47 (s, 3H), 2.68 (dt, *J* = 18.1, 2.5 Hz, 1H), 2.90 (td, *J* = 15.4, 4.2 Hz, 1H), 3.02-3.19 (m, 2H), 3.89-3.91 (m, 6H), 4.02-4.25 (m, 3H), 4.37 (dd, *J* = 11.9, 2.9 Hz, 1H), 6.63 (s, 1H), 6.68 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 15.0, 17.8, 23.0, 27.5, 30.2, 37.6, 44.2, 52.5, 56.2, 56.5, 59.2, 101.5, 109.2, 111.5, 127.5, 130.3, 147.8, 148.0, 153.3, 170.0;

**IR** (NaCl): 2926, 1728, 1604, 1514, 1463, 1254, 1027 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 63.51; H, 6.93; N, 3.75 %.

**Mp**: 73-74 °C.

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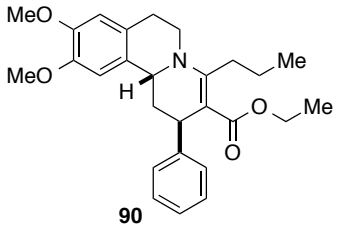
**(±)-(2*S**,11b*S**)-Ethyl 9,10-dimethoxy-2-phenyl-4-propyl-2,6,7,11b-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (90):**




**90**

Prepared from compound 84 (217.5 mg, 0.5 mmol), yield: 167 mg (77 %) as a brown paste. Data of **90**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.00 (t, *J* = 7.0 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.57-2.03 (m, 3H), 2.32 (dt, *J* = 13.1, 3.2 Hz, 1H), 2.66-2.81 (m, 2H), 2.93 (td, *J* = 15.0, 3.7 Hz, 1H), 3.16 (td, *J* = 14.0, 2.8 Hz, 1H), 3.30-3.42 (m, 1H), 3.79-4.00 (m, 8H), 4.08-4.17 (m, 2H), 4.25 (d, *J* = 3.1 Hz, 1H), 6.39 (s, 1H), 6.60 (s, 1H), 7.18-7.33 (m, 5H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 14.7, 22.8, 30.5, 31.9, 38.8, 39.0, 44.1, 52.5, 56.2, 56.5, 59.0, 96.4, 109.3, 111.4, 126.0, 127.4, 128.2, 128.5, 129.9, 147.8, 147.9, 148.2, 159.0, 169.0.

**IR** (NaCl): 2960, 2932, 2871, 1726, 1673, 1602, 1555, 1514, 1453, 1361, 1296, 1298, 1122, 1092 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.30; H, 7.51; N, 3.06 %.

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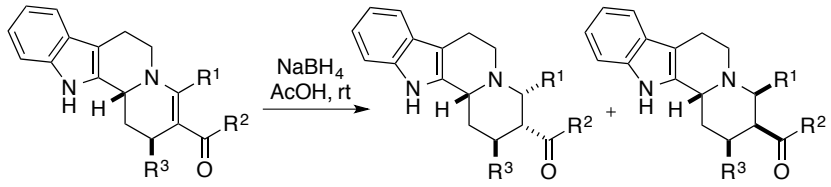
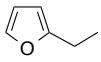
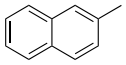
### 7.4.5: General procedure for the STAB reduction

#### 7.4.5.1: Reduction of indolo[2,3-*a*]quinolizine derivatives for the synthesis of compounds 91-114.




| Compds (I,II) | $R^1$ | $R^2$ | $R^3$ | t (h) | Yield (%) | I/II ratio |
|---|---|---|---|---|---|---|
| **91**,**92** | Me | OEt | Ph | 2 | 86 | 40:60 |
| **93**,**94** | Me | OEt | 4-$PhC_6H_4$ | 5 | 85 | 46:54 |
| **95**,**96** | Me | OEt | 4-$ClC_6H_4$ | 2 | 89 | 40:60 |
| **97**,**98** | Me | OEt | 4-$MeOC_6H_4$ | 2 | 90 | 39:61 |
| **99**,**100** | Me | Me | Ph | 3 | 73[a] | 47:53 |
| **101**,**102** | Me | OEt |  | 3 | 80[a] | 39:61 |
| **103**,**104** | Me | S-$^t$Bu | Ph | 1.3 | 85 | 39:61 |
| **105**,**106** | Me | O-$^t$Bu | Ph | 1.3 | 80 | 48:52 |
| **107**,**108** | Me | OEt |  | 72 | 58[a] | 33:57 |
| **109**,**110** | Me | OEt | Me | 2 | 60[a] | 42:58 |
| **111**,**112** | Me | OEt | *n*-Pr | 2 | 68[a] | 40:60 |
| **113**,**114** | *n*-Pr | OEt | Ph | 36 | 65[a] | 35:65 |

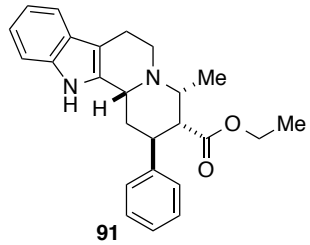
[a]Only the major isomer could be isolated in pure form

Sodium borohydride (6 mmol) was added to stirred glacial acetic acid (3 mL) in three portions, keeping the temperature between 15 and 20 °C, to prepare sodium triacetoxyborohydride, STAB ($NaBH_4(OAc)_3$). After hydrogen evolution had ceased (10 min), the requisite compound (1 mmol)

was added in one portion and the reaction mixture was stirred for the time indicated in the table below. After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with water (10 mL), neutralized with saturated sodium hydrogen carbonate solution, and extracted twice with dichloromethane (20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (gradient from 90:10 to 80:20, v/v). Characterization data for the diastereomers that could be isolated in a pure state are given below.

---

**(±)-(2*R**,3*S**,4*S**,12b*S**)-Ethyl 4-methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (91):**



**91**

Prepared from compound **62** (386 mg, 1 mmol), red solid.

Data of **91**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.00 (t, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 2.06 (td, *J* = 13.1, 4.5 Hz, 1H), 2.28-2.41 (m, 2H), 2.57 (dd, *J* = 15.2, 1.7 Hz, 1H), 2.70-2.82 (m, 1H), 2.96 (quint., *J* = 6.4 Hz, 1H), 3.13 (t, *J* = 5.4 Hz, 1H), 3.22 (ddd, *J* = 11.3, 5.3, 3.3 Hz, 1H), 3.39 (q, *J* = 7.2 Hz, 1H), 3.78 (d, *J* = 11.2 Hz, 1H), 3.84-3.98 (m, 2H), 6.90-7.20 (m, 8H), 7.30-7.34 (m, 1H), 7.6 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 18.5, 22.5, 34.9, 37.0. 48.6, 49.7, 54.4, 56.0, 60.6, 109.0, 111.1, 118.5, 119.7, 121.7, 126.6, 127.5, 127.9, 128.9, 135.7, 136.5, 145.0, 173.0.

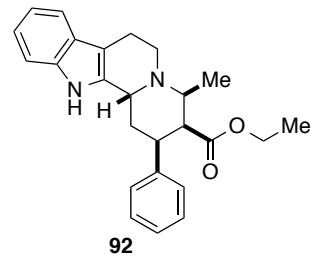
**IR** (NaCl): 3364, 2964, 2928, 2846, 1721, 1453, 1384, 1313, 1262, 1174, 1129, 1028, 909 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{28}N_2O_2$ (M = 388.22): C, 77.29; H, 7.26; N, 7.21. Found: C, 77.15; H, 7.12; N, 7.10 %.

**Mp**: 95-96 °C.

---

**(±)-(2*R**,3*R**,4*R**,12b*S**)-Ethyl 4-methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*] quinolizine-3-carboxylate (92):**




**92**

Prepared from compound **62** (386 mg, 1 mmol), orange solid.

Data of **92**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 0.96 (t, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 2.17 (dd, *J* = 1.6, 13.7 Hz, 1H), 2.57 (dd, *J* = 3.0, 14.8 Hz, 1H), 2.73 (t, *J* = 3.6 Hz, 1H), 2.90 (td, *J* = 3.7, 13.7 Hz, 1H), 3.03 (ddd, *J* = 2.4, 5.1, 15.8 Hz, 1H), 3.21-3.34 (m, 2H), 3.48 (td, *J* = 5.4, 13.7 Hz, 1H), 3.71 (dd, *J* = 4.9, 14.2 Hz, 1H), 3.83-3.99 (m, 2H), 4.86 (d, *J* = 2.6 Hz, 1H), 7.11-7.37 (m, 8H), 7.52-7.55 (m, 1H), 7.83 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.4, 16.4, 19.0, 27.1, 39.9, 48.0, 49.6, 53.3, 55.9, 59.9, 109.7, 111.4, 118.3, 119.9, 121.9, 127.1, 127.8, 128.1, 128.7, 133.5, 135.8, 142.5, 171.7.

**IR** (NaCl): 3381, 2977, 2929, 2845, 2799, 1723, 1601, 1494, 1452, 1383, 1175, 910 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{28}N_2O_2$ (M = 388.22): C, 77.29; H, 7.26; N, 7.21. Found: C, 77.14; H, 7.19; N, 7.02 %.

**Mp**: 177-178 °C.

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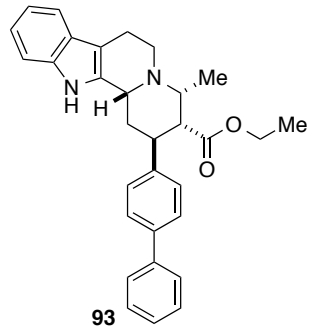
**(±)-(2*R**,3*S**,4*S**,12b*S**)-Ethyl 2-(1,1'-biphenyl-4-yl)-4-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (93):**




**93**

Prepared from compound **64** (231 mg, 0.5 mmol), orange solid.

Data of **93**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.20 (t, *J* = 7.1 Hz, 3H), 1.35 (d, *J* = 6.4 Hz, 3H), 2.30 (dt, *J* = 9.4, 4.5 Hz, 1H), 2.52-2.65 (m, 2H), 2.76 (dd, *J* = 15.0, 1.9 Hz, 1H), 2.90-3.02 (m, 1H), 3.16-3.21 (m, 2H), 3.31-3.45 (m, 2H), 3.59-3.67 (m, 1H), 4.01-4.18 (m, 3H), 7.08-7.18 (m, 2H), 7.36-7.50 (m, 6H), 7.58-7.64 (m, 4H), 7.74 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 18.6, 22.5, 34.9, 36.7, 48.6, 49.7, 54.5, 56.0, 60.7, 109.0, 111.1, 118.5, 119.7, 121.7, 127.4, 127.6, 127.7, 128.4, 129.2, 135.7, 136.5, 139.5, 141.1, 144.1, 173.1 (one quaternary carbon was merged with others).

**IR** (NaCl): 3373, 2929, 1731, 1487, 1453, 1378, 1233, 1175, 1031 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{31}H_{32}N_2O_2$ (M = 464.25): C, 80.14; H, 6.94; N, 6.03. Found: C, 80.08; H, 6.79; N,6.00 %.

**Mp**: 123-124 °C.

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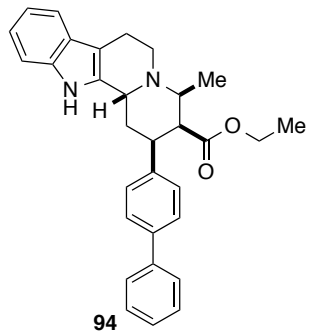
**(±)-(2*R**,3*R**,4*R**,12b*S**)-Ethyl 2-(1,1'-biphenyl-4-yl)-4-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (94):**




**94**

Prepared from compound **64** (231 mg, 0.5 mmol), orange solid.

Data of **94**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 0.97 (t, *J* = 6.9 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H), 2.22 (d, *J* = 13.2 Hz,

1H), 2.58 (d, *J* = 15.1 Hz, 1H), 2.77 (s, 1H), 2.92-2.98 (m, 2H), 3.30 (s, 1H), 3.48-3.76 (m, 3H), 3.92 (q, *J* = 6.9 Hz, 2H), 4.89 (bs, 1H), 7.17-7.61 (m, 13H), 7.85 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 16.4, 19.1, 27.2, 39.6, 48.0, 49.6, 53.2, 55.9, 60.0, 109.8, 111.4, 118.4, 120.0, 121.9, 127.3, 127.4, 127.6, 128.1, 128.2, 129.2, 133.4, 135.8, 140.0, 141.1, 141.6, 171.7.

**IR** (NaCl) 3350, 2929, 1715, 1487, 1453, 1383, 1314, 1263, 1173, 1068 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{31}H_{32}N_2O_2$ (M = 464.25): C, 80.14; H, 6.94; N, 6.03. Found: C, 80.02; H, 6.73; N, 5.84 %.

**Mp**: 124-125 °C.

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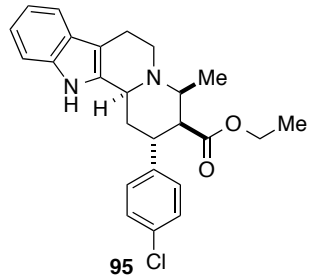
**(±)-(2*R**,3*S**,4*S**,12b*S**)-Ethyl 2-(4-chlorophenyl)-4-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (95):**



**95**

Prepared from compound 65 (210 mg, 0.5 mmol), red solid.

Data of **95**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.19 (t, *J* = 7.1 Hz, 3H), 1.31 (d, *J* = 6.5 Hz, 3H), 2.11-2.23 (m, 1H), 2.44-2.58 (m, 2H), 2.75 (dd, *J* = 13.4, 1.8 Hz, 1H), 2.88-3.01 (m, 1H), 3.13 (quint., *J* = 6.3 Hz, 1H), 3.27 (dd, *J* = 7.7, 5.6 Hz, 1H), 3.40 (ddd, *J* = 11.2, 5.2, 2.0 Hz, 1H), 3.50-3.59 (m, 1H), 3.98-4.15 (m, 3H), 7.08-7.18 (m, 2H), 7.23-7.35 (m, 5H), 7.48-7.51 (m, 1H), 7.69 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 18.3, 22.5, 35.3, 36.4, 48.8, 49.5, 54.1, 56.1, 60.8, 109.1, 111.1, 118.5, 119.8, 121.8, 127.5, 129.0, 129.3, 132.3, 135.5, 136.5. 143.7, 172.7.

**IR** (NaCl): 2927, 1731, 1622, 1531, 1493, 1470, 1372, 1328, 1290, 1233, 1176, 1091, 1015 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{27}ClN_2O_2$ (M = 422.18): C, 70.99; H, 6.43; N, 6.62. Found: C, 70.86; H, 6.22; N, 6.59 %.

**Mp**: 120-121 °C.

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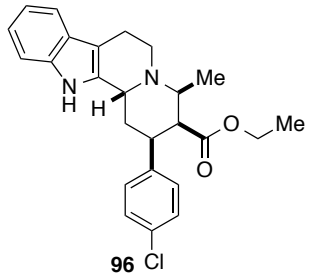
**(±)-(2*R**,3*R**,4*R**,12b*S**)-Ethyl 2-(4-chlorophenyl)-4-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (96):**



**96**

Prepared from compound **65** (210 mg, 0.5 mmol), orange solid.

Data of **96**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.02 (t, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 6.4 Hz, 3H), 2.14 (d, *J* = 14.8 Hz, 1H), 2.57 (dd, *J* = 16.0, 3.8 Hz, 1H), 2.69 (t, *J* = 3.8 Hz, 1H), 2.86 (dt, *J* = 13.7, 3.8 Hz, 1H), 2.94-3.07 (m, 1H), 3.21-3.33 (m, 2H), 3.45 (td, *J* = 13.6, 5.0 Hz, 1H), 3.70 (dd, *J* = 14.1, 5.0 Hz, 1H), 3.91 (q, *J* = 7.1 Hz, 2H), 4.85 (s, 1H), 7.12-7.22 (m, 4H), 7.27-7.36 (m, 3H), 7.52-7.55 (m, 1H), 7.80 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 16.4, 19.1, 27.2, 39.4, 48.0, 49.6, 53.1, 55.8, 60.1, 109.8, 111.4, 118.4, 120.0, 121.9, 128.0, 128.8, 129.2, 132.9, 133.3, 135.8, 141.1, 171.6.

**IR** (NaCl) 3370, 3054, 2977, 2934, 2845, 1715, 1491, 1453, 1406, 1314, 1262, 1173, 1067, 1014 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{27}ClN_2O_2$ (M = 422.18): C, 70.99; H, 6.43; N, 6.62. Found: C, 70.82; H, 6.32; N, 6.83 %.

**Mp**: 245-246 °C.

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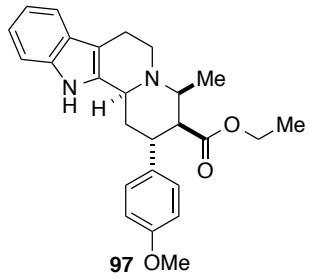
**(±)-(2*R**,3*S**,4*S**,12b*S**)-Ethyl 2-(4-methoxyphenyl)-4-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (97):**




Prepared from compound **66** (208 mg, 0.5 mmol), orange solid.

Data of **97**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.20 (t, *J* = 7.1 Hz, 3H), 1.31 (d, *J* = 6.4 Hz, 3H), 2.18-2.32 (m, 1H), 2.47-2.60 (m, 2H), 2.74 (dd, *J* = 13.2, 1.5 Hz, 1H), 2.87-3.01 (m, 1H), 3.13 (quint., *J* = 6.3 Hz, 1H), 3.25 (t, *J* = 5.3 Hz, 1H), 3.36-3.43 (m, 1H), 3.53 (q, *J* = 7.0 Hz, 1H), 3.83 (s, 3H), 3.96-4.16 (m, 3H), 6.86-6.93 (m, 2H), 7.07-7.18 (m, 2H), 7.26-7.31 (m, 3H), 7.47-7.51 (m, 1H), 7.71 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 18.6, 22.5, 35.0, 36.2, 48.5, 50.0, 54.5, 55.6, 55.9, 60.6, 109.0, 111.0, 114.3, 118.5, 119.7, 121.7, 127.6, 128.9, 135.8, 136.5, 137.0, 158.2, 173.1.

**IR** (NaCl): 2918, 2845, 1731, 1608, 1514, 1464, 1378, 1248, 1178 $cm^{-1}$;

**Elemental analysis**: Anal. Calcd for $C_{26}H_{30}N_2O_3$ (M = 418.23): C, 74.61; H, 7.22; N, 6.69. Found: C, 74.57; H, 7.08; N, 6.77 %.

**Mp**: 119-120 °C.

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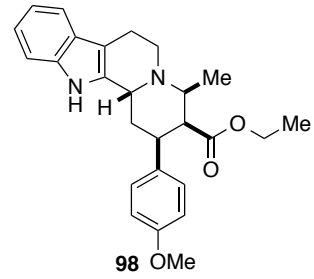
**(±)-(2*R**,3*R**,4*R**,12b*S**)-Ethyl 2-(4-methoxyphenyl)-4-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (98):**




Prepared from compound **66** (208 mg, 0.5 mmol), as an orange solid.

Data of **98**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.00 (t, *J* = 7.1 Hz, 3H), 1.29 (d, *J* = 6.4 Hz, 3H), 2.15 (d, *J* = 13.0 Hz, 1H), 2.52-2.59 (m, 1H), 2.69 (t, *J* = 3.8 Hz, 1H), 2.84 (dd, *J* = 10.0, 3.7 Hz,

1H), 2.94-3.05 (m, 1H), 3.20-3.33 (m, 2H), 3.38-3.53 (m, 1H), 3.64-4.03 (m, 6H), 4.84 (d, *J* = 1.9 Hz, 1H), 6.78-6.86 (m, 2H), 7.13-7.28 (m, 5H), 7.48-7.55 (m, 1H), 7.90 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 16.4, 19.1, 27.4, 39.1, 48.0, 49.5, 53.4, 55.6, 55.9, 59.9, 109.7, 111.4, 114.1, 118.3, 119.9, 121.8, 128.0, 128.7, 133.6, 134.7, 135.8, 158.7, 171.8.

**IR** (NaCl): 3361, 2973, 2932, 1722, 1611, 1513, 1454, 1248, 1176 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{26}H_{30}N_2O_3$ (M = 418.23): C, 74.61; H, 7.22; N, 6.69. Found: C, 74.77; H, 6.09; N, 6.54 %.

**Mp**: 130-131 °C.

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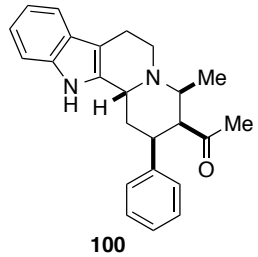
**(±)-(2*R**,3*R**,4*R**,12b*S**)-4-Methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydro indolo[2,3-*a*] quinolizin-3-yl)ethanone (100):**



**100**

Prepared from compound **75** (178 mg, 0.5 mmol), orange solid.

Data of **100**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.27 (d, *J* = 6.5 Hz, 3H), 1.64 (s, 3H), 2.16 (d, *J* = 13.5 Hz, 1H), 2.55 (dd, *J* = 15.8, 3.1 Hz, 1H), 2.92-3.02 (m, 3H), 3.15-3.34 (m, 3H), 3.70 (dd, *J* = 14.3, 4.9 Hz, 1H), 4.88 (s, 1H), 7.16-7.33 (m, 8H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.91 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 16.2, 18.9, 26.9, 36.2, 40.4, 47.8, 49.8, 55.8, 58.7, 109.7, 111.4, 118.3, 120.0, 121.9, 127.4, 127.6, 128.0, 129.1, 133.3, 135.8, 142.3, 211.1.

**IR** (NaCl) 3358, 2923, 1706, 1494, 1453, 1351, 1312, 1263, 1180 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{24}H_{26}N_2O$ (M = 358.20): C, 80.41; H, 7.31; N, 7.81. Found: C, 80.29; H, 7.14; N, 7.70 %.

**Mp**: 175-176 °C.

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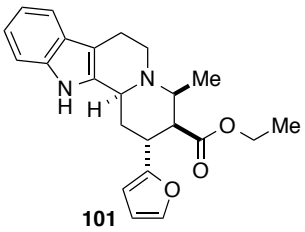
**(±)-(2*R**,3*S**,4*S**,12b*S**)-ethyl 2-(furan-2-yl)-4-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (101):**



**101**

Prepared from compound **68** (188 mg, 0.5 mmol), brown solid.

Data of **101**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.30 (t, *J* = 7.1 Hz, 3H), 1.43 (d, *J* = 6.4 Hz, 3H), 2.35-2.40 (m, 2H), 2.57-2.76 (m, 2H), 2.84-2.96 (m, 1H), 3.06-3.10 (m, 2H), 3.39 (td, *J* = 8.5, 3.8 Hz, 1H), 3.66 (d, *J* = 4.9 Hz, 1H), 3.82 (d, *J* = 11.2 Hz, 1H), 4.22 (d, *J* = 7.1 Hz, 2H), 6.22 (d, *J* = 2.3 Hz, 1H), 6.38 (s, 1H), 7.06-7.17 (m, 2H), 7.28-7.34 (m, 1H), 7.40 (s, 1H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.87 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.7, 19.6, 22.5, 29.9, 34.4, 46.1, 48.5, 55.4, 56.3, 60.7, 106.4, 109.1, 110.7, 111.1, 118.4, 119.7, 121.6, 127.7, 135.6, 136.4, 141.5, 156.9, 173.0.

**IR** (NaCl) 3387, 2924, 1726, 1453, 1378, 1308, 1177, 1112, 1015 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{23}H_{26}N_2O_3$ (M = 378.19): C, 72.99; H, 6.92; N, 7.40. Found: C, 72.82; H, 7.03; N, 7.33 %.

**Mp**: 120-121 °C.

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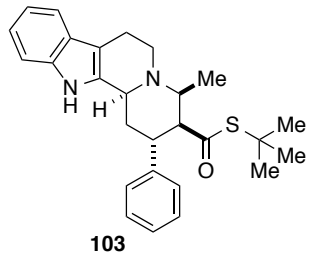
**(±)-(2*R**,3*S**,4*S**,12b*S**)-*S*-*tert*-Butyl 4-methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carbothioate (103):**



**103**

Prepared from compound 72 (215 mg, 0.5 mmol), brown solid.

Data of **103**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.29-1.39 (m, 12H),

2.16-2.23 (m, 1H), 2.39-2.58 (m, 2H), 2.75 (d, *J* = 15.3 Hz, 1H), 2.91-3.03 (m, 1H), 3.11-3.18 (m, 1H), 3.39-3.56 (m, 3H), 3.97 (d, *J* = 9.0 Hz, 1H), 7.07-7.14 (m, 2H), 7.24-7.36 (m, 6H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.68 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 17.8, 22.5, 29.9, 35.8, 37.2, 48.6, 49.1, 53.7, 56.8, 57.6, 109.1, 111.0, 118.5, 119.7, 121.7, 126.7, 127.6, 127.9, 128.9, 135.6, 136.5, 144.7, 199.5.

**IR** (NaCl): 2923, 1673, 1454, 1162 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{32}N_2OS$ (M = 432.22): C, 74.96; H, 7.46; N, 6.48; S, 7.41. Found: C, 74.85; H, 7.30; N, 6.31; S, 7.25 %.

**Mp**: 125-126 °C.

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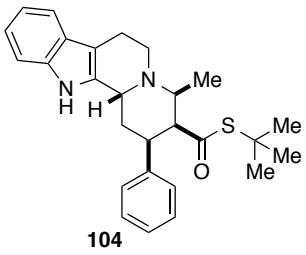
**(±)-(2*R**,3*R**,4*R**,12b*S**)-*S*-*tert*-butyl 4-methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carbothioate (104):**



**104**

Prepared from compound **72** (215 mg, 0.5 mmol), orange solid.

Data of **104**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.27 (s, 9H), 1.37 (d, *J* = 6.5 Hz, 3H), 2.14-2.20 (m, 1H), 2.56 (dd, *J* = 15.1, 2.6 Hz, 1H), 2.79-2.74 (m, 1H), 2.84-3.03 (m, 2H), 3.24-3.43 (m, 3H), 3.72 (dd, *J* = 13.9, 4.7 Hz, 1H), 4.89 (bs, 1H), 7.11-7.19 (m, 3H), 7.25-7.35 (m, 5H), 7.51-7.54 (m, 1H), 7.79 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 16.3, 19.0, 27.8, 29.6, 41.0, 48.0, 48.5, 50.2, 55.8, 60.8, 109.8, 111.3, 118.4, 120.0, 121.9, 127.2, 128.1, 128.7, 133.4, 135.8, 141.9. 199.9 (one quaternary carbon is merged with the others).

**IR** (NaCl): 2924, 1667, 1454, 1165 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{32}N_2OS$ (M = 432.22): C, 74.96; H, 7.46; N, 6.48; S, 7.41. Found: C, 74.73; H, 7.72; N, 6.17; S, 6.89 %.

**Mp**: 148-149 °C.

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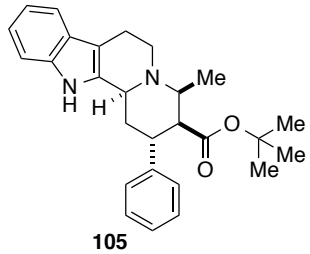
**(±)-(2*R**,3*S**,4*S**,12b*S**)-*tert*-Butyl 4-methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2, 3-*a*]quinolizine-3-carboxylate (105):**




**105**

Prepared from compound **73** (207 mg, 0.5 mmol), orange solid.

Data of **105**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.30-1.35 (m, 12H), 2.14-2.24 (m, 1H), 2.39-2.60 (m, 2H), 2.77 (dd, *J* = 15.2, 1.8 Hz, 1H), 2.89-3.02 (m, 1H), 3.14-3.21 (m, 1H), 3.27-3.33 (m, 1H), 3.38-3.55 (m, 2H), 4.04 (dd, *J* = 11.0, 2.6 Hz, 1H), 7.10-7.18 (m, 2H), 7.23-7.39 (m, 6H), 7.49-7.51 (m, 1H), 7.68 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 18.0, 22.5, 28.2, 36.2, 36.8, 49.2, 50.0, 53.7, 56.5, 81.1, 108.8, 111.1, 118.5, 119.7, 121.6, 126.5, 127.5, 127.9, 128.9, 135.9, 136.5, 145.6, 172.2.

IR (NaCl) 2976, 1722, 1455, 1368, 1251, 1153 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{32}N_2O_2$ (M = 416.25): C, 77.85; H, 7.74; N, 6.73. Found: C, 77.76; H, 7.55; N, 6.55 %.

**Mp**: 115-116 °C.

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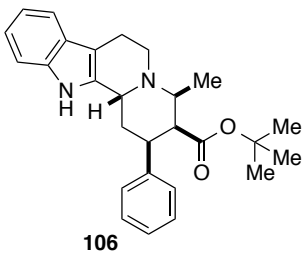
**(±)-(2*R**,3*R**,4*R**,12b*S**)-*tert*-Butyl 4-methyl-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (106):**




**106**

Prepared from compound **73** (207 mg, 0.5 mmol), yellow solid.

Data of **106**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.18 (s, 9H), 1.32 (d, *J* = 6.3 Hz, 3H), 2.17 (d, *J* = 13.7 Hz, 1H), 2.53-2.65 (m, 2H), 2.85-3.07 (m, 2H), 3.23-3.35 (m, 2H), 3.46 (td, *J* = 13.7, 5.3 Hz,

1H), 3.72 (dd, *J* = 14.1, 4.8 Hz, 1H), 4.88 (bs, 1H), 7.12-7.35 (m, 8H), 7.55 (d, *J* = 3.6 Hz, 1H), 7.81 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 16.3, 18.9, 26.9, 28.2, 39.7, 47.9, 49.5, 53.4, 55.8, 80.3, 109.7, 111.4, 118.3, 119.9, 121.8, 127.0, 128.0, 128.1, 128.6, 133.7, 135.8, 142.5, 171.1.

**IR** (NaCl): 3364, 2975, 2932, 1713, 1452, 1399, 1366, 1312, 1263, 1216, 1150, 1066 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{32}N_2O_2$ (M = 416.25): C, 77.85; H, 7.74; N, 6.73. Found: C, 77.78; H, 7.51; N, 6.61 %.

**Mp**: 240-241 °C.

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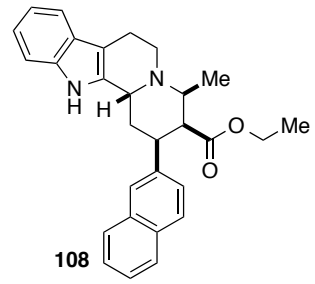
**(±)-(2*R**,3*R**,4*R**,12b*S**)-Ethyl 4-methyl-2-(naphthalen-1-yl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (108):**



**108**

Prepared from compound **69** (218 mg, 0.5 mmol), orange solid.

Data of **108**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 0.80 (t, *J* = 7.1 Hz, 3H), 1.33 (d, *J* = 6.5 Hz, 3H), 2.22 (d, *J* = 10.7 Hz, 1H), 2.63 (dd, *J* = 15.4, 3.6 Hz, 1H), 2.99-3.14 (m, 2H), 3.28-3.57 (m, 2H), 3.71-3.89 (m, 5H), 4.98 (bs, 1H), 7.14-7.20 (m, 2H), 7.38-7.59 (m, 6H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.85-7.89 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ (one quaternary carbon merged) 14.35, 16.4, 19.0, 27.5, 35.1, 48.2, 49.8, 51.8, 56.3, 59.8, 109.7, 111.5, 118.3, 119.9, 121.9, 123.0, 124.3, 125.8, 125.9, 126.6, 127.8, 128.1, 129.4, 131.6, 134.1, 136.0, 137.8, 171.4

**IR** (NaCl): 3361, 3053, 2977, 2358, 1722, 1597, 1510, 1453, 1384, 1314, 1263, 1179, 1129, 1070, 1026 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{29}H_{30}N_2O_2$ (M = 338.23): C, 79.42; H, 6.89; N, 6.39. Found: C, 79.34; H, 6.70; N, 6.19 %.

**Mp**: 132-133 °C.

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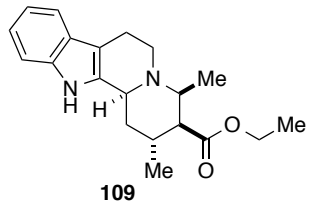
**(±)-(2*R**,3*S**,4*S**,12b*S**)-Ethyl 2,4-dimethyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine-3-carboxylate (109):**




**109**

Prepared from compound **70** (162 mg, 0.5 mmol), yellow solid.

Data of **109**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.24-1.37 (m, 9H), 1.73 (d, *J* = 12.0 Hz, 2H), 2.41-2.52 (m, 3H), 2.72 (d, *J* = 15.8 Hz, 1H), 2.85-2.93 (m, 1H), 3.06 (s, 1H), 3.40-3.45 (m, 1H), 3.75 (d, *J* = 9.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 7.06-7.18 (m, 2H), 7.29-7.34 (m, 1H), 7.49 (d, *J* = 6.9 Hz, 1H), 7.72 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.7, 19.5, 19.7, 22.5, 28.5, 33.4, 46.8, 51.8, 53.9, 54.8, 60.4, 109.0, 111.1, 118.4, 119.6, 121.5, 127.8, 136.0, 136.4, 173.9.

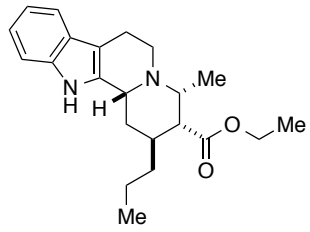
**IR** (NaCl): 3373, 2920, 2351, 1721, 1454, 1380, 1310, 1279, 1216, 1172, 1087, 1028 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{20}H_{26}N_2O_2$ (M = 326.20): C, 73.59; H, 8.03; N, 8.58. Found: C, 73.47; H, 7.99; N, 8.50 %.

**Mp**: 168-169 °C.

---

**(±)-(2*R**,3*S**,4*S**,12b*S**)-Ethyl 4-methyl-2-propyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (111):**



**111**

Prepared from compound **71** (176 mg, 0.5 mmol), yellow solid.

Data of **111**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.00 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.41-1.51 (m, 2H), 1.53-1.64 (m, 2H), 1.80 (d, *J* = 12.8 Hz, 1H), 2.21-2.23 (m, 1H), 2.32-2.48 (m, 3H), 2.71 (d, *J* = 15.2 Hz, 1H), 2.85-3.01 (m, 2H), 3.42 (ddd, *J* = 11.0, 5.1, 2.6 Hz, 1H), 3.67 (d, *J* = 12.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 7.06-7.18 (m, 2H), 7.29-7.34 (m, 1H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.73 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.6, 14.7, 19.6, 21.2, 22.5, 31.5, 33.8, 35.3, 46.8, 50.4, 54.3, 55.3, 60.3, 109.1, 111.0, 118.4, 119.6, 121.5, 127.8, 136.0, 136.4, 173.9.

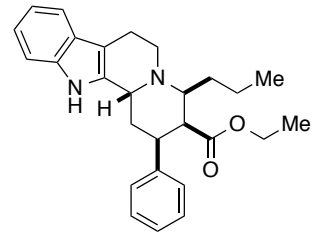
**IR** (NaCl): 3380, 2957, 2928, 2791, 1722, 1625, 1454, 1384, 1307, 1271, 1178, 1093, 1030 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{22}H_{30}N_2O_2$ (M = 354.23): C, 74.54; H, 8.53; N, 7.90. Found: C, 74.44; H, 8.49; N, 8.03 %.

**Mp**: 138-139 °C.

---

**(±)-(2*R**,3*R**,4*R**,12b*S**)-Ethyl 2-phenyl-4-propyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3*a*]quinolizine-3-carboxylate (114):**



**114**

Prepared from compound **74** (207 mg, 0.5 mmol), orange solid.

Data of **114**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 0.91-0.98 (m, 6H),

1.22-1.41 (m, 2H), 1.55-1.65 (m, 1H), 1.90-2.00 (m, 1H), 2.15 (d, *J* = 14.2 Hz, 1H), 2.56 (dd, *J* = 15.7, 3.9 Hz, 1H), 2.82-3.05 (m, 3H), 3.07-3.13 (m, 1H), 3.27 (td, *J* = 12.7, 4.7 Hz, 1H), 3.46 (td, *J* = 13.5, 5.3 Hz, 1H), 3.83 (q, *J* = 7.0 Hz, 2H), 3.90-4.03 (m, 1H), 4.88 (bs, 1H), 6.87-7.38 (m, 8H), 7.51-7.55 (m, 1H), 7.56 (s, 1H).

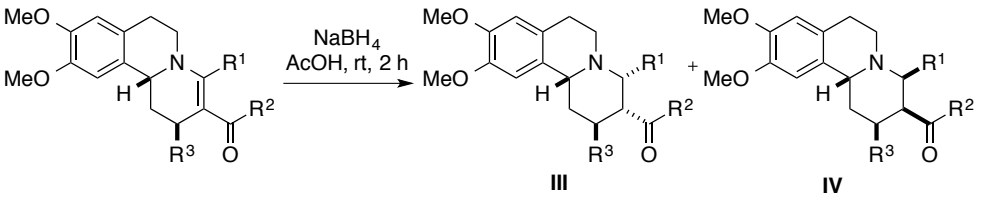
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.3, 14.9, 16.6, 19.4, 27.0, 33.9, 40.0, 48.1, 49.7, 54.5, 56.4, 59.8, 109.7, 111.4, 118.4, 119.9, 121.8, 127.2, 127.8, 128.1, 128.7, 133.6, 135.8, 142.7, 171.7.

**IR** (NaCl): 3354, 2959, 1716, 1454, 1311, 1261, 1174, 1029 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{32}N_2O_2$ (M = 416.25): C, 77.85; H, 7.74; N, 6.73. Found: C, 77.79; H, 7.59; N, 6.68 %.

**Mp**: 202-203 °C.

### 7.4.5.2. Reduction of benzo[*a*]quinolizine derivatives to compounds 115-124




| Compds (I,II) | $R^1$ | $R^2$ | $R^3$ | Yield (%) | I/II ratio |
|---|---|---|---|---|---|
| **115,116** | Me | OEt | Ph | 90[a] | 38:62 |
| **117,118** | Me | OEt | *p*-$ClC_6H_4$ | 92 | 35:65 |
| **119,120** | Me | OEt | *p*-$MeOC_6H_4$ | 82[a] | 32:68 |
| **121,122** | *n*-Pr | OEt | Ph | 78 | 35:65 |
| **123,124** | Me | OEt | Me | 79[a] | 35:65 |

[a]Only one isomer could be isolated in pure form

The procedure is the same as in 7.4.5.1. The crude products were purified by flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (gradient from 90:10 to 80:20, v/v). Characterization data for the obtained products are given below.

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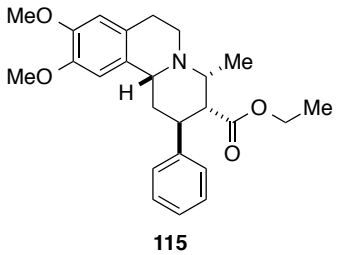
**(±)-(2*R**,3*S**,4*S**,11b*S**)-Ethyl 9,10-dimethoxy-4-methyl-2-phenyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (115)**




**115**

Prepared from compound **85** (203 mg, 0.5 mmol), brown solid.

Data of **115**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.27 (t, *J* = 7.1 Hz, 3H), 1.39 (d, *J* = 6.5 Hz, 3H), 2.44-2.62 (m, 3H),

2.77 (d, *J* = 16.1 Hz, 1H), 3.06-3.23 (m, 2H), 3.34-3.43 (m, 2H), 3.66 (q, *J* = 7.0 Hz, 1H), 3.95-4.08 (m, 7H), 4.20 (q, *J* = 7.1 Hz, 2H), 6.71 (d, *J* = 4.1 Hz, 2H), 7.34-7.41 (m, 1H), 7.48-7.49 (m, 4H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 17.9, 30.0, 37.3, 37.5, 47.6, 49.2, 56.2, 56.4, 56.5, 57.2, 60.5, 108.8, 111.4, 126.5, 127.2, 127.9, 128.9, 131.4, 145.7, 147.6, 147.7, 173.2.

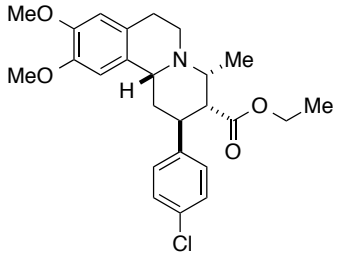
**IR** (NaCl): 2931, 1731, 1603, 1514, 1463, 1254, 1027 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{25}H_{31}NO_4$ (M = 409.23): C, 73.32; H, 7.63; N, 3.42. Found: C, 73.17; H, 7.57; N, 3.34 %.

**Mp**: 78-79 °C.

---

**(±)-(2*R**,3*S**,4*S**,11b*S**)-Ethyl 2-(4-chlorophenyl)-9,10-dimethoxy-4-methyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (117):**




**117**

Prepared from compound **87** (220 mg, 0.5 mmol), yellow solid.

Data of **117**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.16 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 6.4 Hz, 3H), 2.28-2.34 (m, 2H), 2.45 (td, *J* = 11.5, 2.3 Hz, 1H), 2.65 (d, *J* = 15.9 Hz, 1H), 2.94-3.08 (m, 2H), 3.22-3.28 (m, 2H), 3.51 (q, *J* = 7.2 Hz, 1H), 3.83-3.90 (m, 7H), 3.99-4.13 (m, 2H), 6.57-6.59 (m, 2H), 7.26-7.35 (m, 4H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 17.7, 30.0, 36.8, 37.9, 47.8, 49.1, 56.2, 56.4, 56.5, 57.0, 60.7, 108.7, 111.4, 127.1, 129.0, 129.3, 131.2, 132.2, 144.2, 147.7, 147.8, 172.9.

**IR** (NaCl): 2919, 1731, 1254, 1166, 1091, 1028 $cm^{-1}$.

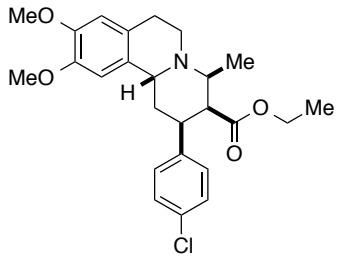
**Elemental analysis**: Anal. Calcd for : $C_{25}H_{30}ClNO_4$ (M = 443.19): C, 67.63; H,

6.81; N, 3.15. Found: C, 67.55; H, 6.70; N, 3.04 %.

**Mp**: 87-88 °C.

---

**(±)-(2*R**,3*R**,4*R**,11b*S**)-Ethyl 2-(4-chlorophenyl)-9,10-dimethoxy-4-methyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (118):**




**118**

Prepared from compound **87** (220 mg, 0.5 mmol), as a yellow solid.

Data of **118**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 1.01 (t, *J* = 7.1 Hz, 3H), 1.26 (d, *J* = 6.7 Hz, 3H), 2.35-2.49 (m, 2H), 2.70 (t, *J* = 4.2 Hz, 1H), 2.93 (dt, *J* = 4.6, 13.4 Hz, 1H), 3.00-3.09 (m, 1H), 3.15 (dd, *J* = 4.2, 6.3 Hz, 1H), 3.22-3.30 (m, 1H), 3.36 (dd, *J* = 4.9, 13.5 Hz, 1H), 3.57 (dd, *J* = 5.7, 14.1 Hz, 1H), 3.78 (s, 3H), 3.83-4.02 (m, 5H), 4.62 (bs, 1H), 6.65 (s, 1H), 6.70 (s, 1H), 7.17-7.20 (m, 2H), 7.26-7.30 (m, 2H);

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 18.6, 22.2, 27.1, 38.6, 47.6, 49.3, 53.1, 53.8, 56.2, 56.5, 58.3, 60.0, 77.6, 108.9, 112.4, 128.8, 129.2, 132.7, 141.5, 147.9, 148.0, 171.5;

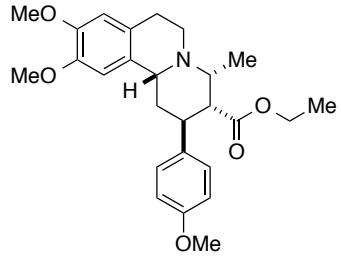
**IR** (NaCl): 2925, 2854, 2358, 1732, 1607, 1513, 1493, 1463, 1256, 1208, 1174, 1101, 1014 $cm^{-1}$;

**Elemental analysis**: Anal. Calcd for $C_{25}H_{30}ClNO_4$ (M = 443.19): C, 67.63; H, 6.81; N, 3.15. Found: C, 67.55; H, 6.72; N, 3.01 %.

**Mp**: 68-69 °C.

---

**(±)-(2*R**,3*S**,4*S**,11b*S**)-Ethyl 9,10-dimethoxy-2-(4-methoxyphenyl)-4-methyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (119):**




**119**

Prepared from compound **88** (218 mg, 0.5 mmol), pale brown paste.

Data of **119**:

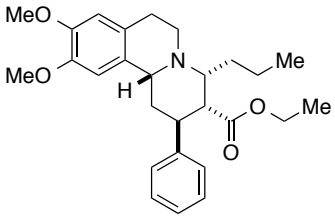
**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.17 (t, *J* = 7.1 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 2.31-2.48 (m, 3H), 2.65 (d, *J* = 16.0 Hz, 1H), 2.94-3.09 (m, 2H), 3.19-3.29 (m, 2H), 3.49 (q, *J* = 7.3 Hz, 1H), 3.81-3.94 (m, 10 H), 4.08 (d, *J* = 7.1 Hz, 2H), 6.59 (d, *J* = 5.0 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.26-7.30 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 17.9, 30.0, 36.6, 37.4, 47.4, 49.5, 55.6, 56.2, 56.3, 56.4, 57.2, 60.5, 108.8, 111.4, 114.2, 127.1, 128.9, 131.4, 137.6, 147.5, 147.6, 158.2, 173.3.

**IR** (NaCl): 2935, 2835, 1731, 1645, 1610, 1514, 1464, 1381, 1253, 1177, 1031 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{26}H_{33}NO_5$ (M = 439.24): C, 71.05; H, 7.57; N, 3.19. Found: C, 65.96; H, 6.92; N, 2.98 %.

**(±)-(2*R**,3*S**,4*S**,11b*S**)-Ethyl 9,10-dimethoxy-2-phenyl-4-propyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (121)**




**121**

Prepared from compound **90** (217 mg, 0.5 mmol) obtained as a brown solid.

Data of **121**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 0.93 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.35-1.47 (m, 2H), 1.67-1.79 (m, 2H), 2.23 (dt, *J* = 14.2, 3.5 Hz, 1H), 2.46-2.59 (m, 1H), 2.70-2.90 (m, 4H), 3.08-3.18 (m, 3H), 3.63-3.69 (m, 1H), 3.81-3.97 (m, 6H), 4.17 (q, *J* = 7.1 Hz, 2H), 6.56-6.62 (m, 2H), 7.24-7.29 (m, 2H), 7.36-7.44 (m, 3H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.5, 14.6, 20.6, 30.3, 33.1, 34.6, 38.3, 43.4, 46.4, 56.2, 56.5, 56.9, 60.1, 60.7, 109.4, 111.7, 126.5, 127.4, 127.9, 129.0, 147.5, 147.8, 174.4.

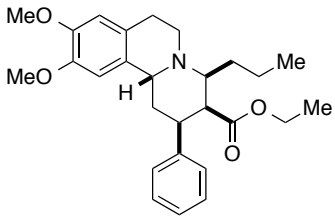
**IR** (NaCl): 2959, 1728, 1650, 1602, 1516, 1464, 1377, 1275, 1174 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{35}NO_4$ (M = 437.26): C, 74.11; H, 8.06; N, 3.20. Found: C, 74.00; H, 8.01; N, 3.16 %.

**Mp**: 78-79 °C.

---

**(±)-(2*R**,3*R**,4*R**,11b*S**)-Ethyl 9,10-dimethoxy-2-phenyl-4-propyl-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate (122):**




**122**

Prepared from compound **90** (217 mg, 0.5 mmol) obtained as a brown paste.

Data of **122**:

**$^1$H NMR** ($CDCl_3$, 250 MHz): δ 0.90-0.96 (m, 6H), 1.22-1.37 (m, 2H), 1.79-1.94 (m, 1H), 2.37-2.48 (m, 2H), 2.87-3.06 (m, 4H), 3.21-3.40 (m, 2H), 3.66 (dd, *J* = 14.3, 5.6 Hz, 1H), 3.75-3.99 (m, 9H), 4.64 (bs, 1H), 6.66 (s, 1H), 6.72 (s, 1H), 7.23-7.35

(m, 5H).

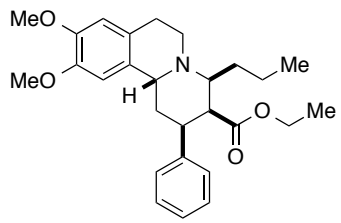
**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.3, 14.9, 19.4, 22.6, 26.9, 33.7, 39.2, 47.7, 49.7, 54.3, 56.2, 56.6, 58.8, 59.7, 109.2, 112.4, 127.0, 127.8, 128.3, 128.5, 128.7, 143.3, 147.8, 148.0, 171.6.

**IR** (NaCl): 2927, 1732, 1514, 1463, 1256, 1161, 1029 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{27}H_{35}NO_4$ (M = 437.26): C, 74.11; H, 8.06; N, 3.20. Found: C, 74.01; H, 8.19; N, 2.98 %.

---

**(±)-(2*R**,3*R**,4*R**,11b*S**)-Ethyl 9,10-dimethoxy-2,4-dimethyl-2,3,4,6,7, 11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-3-carboxylate(124)**




**124**

Prepared from compound 89 (172 mg, 0.5 mmol), brown paste.

Data of **124**:

**$^{1}$H NMR** ($CDCl_3$, 250 MHz): δ 1.25-1.33 (m, 9H), 1.73 (d, *J* = 13.2 Hz, 1H), 2.24-2.34 (m, 2H), 2.37-2.47 (m, 2H), 2.66 (dt, *J* = 15.7, 4.4 Hz, 1H), 2.84-2.96 (m, 1H), 3.10 (dd, *J* = 6.7, 4.4 Hz, 1H), 3.18-3.26 (m, 1H), 3.71 (d, *J* = 10.5 Hz, 1H), 3.86-3.95 (m, 6H), 4.09-4.22 (m, 2H), 6.57-6.60 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz): δ 14.7, 18.7, 19.9, 29.0, 30.0, 34.4, 43.9, 50.5, 53.9, 56.2, 56.4, 57.2, 60.3, 109.1, 111.5, 127.5, 131.2, 147.4, 147.6, 174.2;

**IR** (NaCl): 2935, 1730, 1650, 1604, 1517, 1464, 1379, 1341, 1257, 1174, 1127, 1086, 1029 $cm^{-1}$.

**Elemental analysis**: Anal. Calcd for $C_{20}H_{29}NO_4$ (M = 347.21): C, 69.14; H, 8.41; N, 4.03; Found: C, 69.04; H, 8.35; N, 3.89 %.

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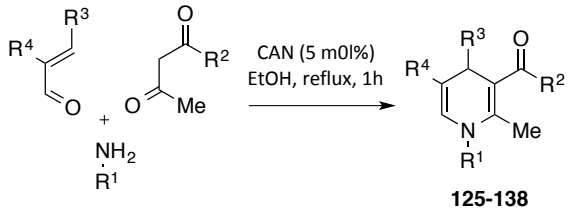
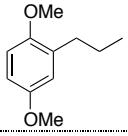
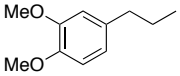
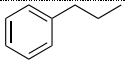
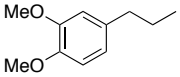
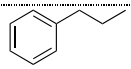
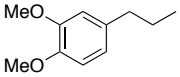
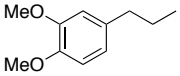
## 7.5: Synthesis of piperidines based on a multicomponent reaction.

### 7.5.1: Synthesis of 2,3,4,5-substituted dihydropyridine (DHP) derivatives.




**125-138**

| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| **125** |  | Me | OEt | Ph | H |
| **126** |  | Me | OEt | Ph | H |
| **127** |  | Me | OEt | *p*-$MeC_6H_4$ | H |
| **128** |  | Me | OEt | *p*-$MeOC_6H_4$ | H |
| **129** | *n*-Pr | Me | O-$^t$Bu | *p*-$NO_2C_6H_4$ | H |
| **130** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H |
| **131** | Bn | Me | OEt | *p*-$NO_2C_6H_4$ | H |
| **132** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H |
| **133** | *n*-Bu | Me | OEt | *o*-$NO_2C_6H_4$ | H |
| **134** |  | Me | OEt | Et | Me |
| **135**[a] | Bn | Me | OEt | Me | H |
| **136** | *n*-Pr | Me | OEt | Me | H |
| **137**[a] | *n*-Bu | Me | OEt | Me | H |
| **138**[b] |  | Me | OEt | H | Me |

[a]Known compounds. Their spectral data are reported in reference 20.
[b]After column, a mixture of **138** and the corresponding tetrahydropyridine was obtained, which was employed for the reduction step without separation

A solution of the primary amine (1 mmol), β-ketoester (1 mmol) and CAN (5 mol%) in ethanol (3 mL) was refluxed for 30 min. The suitable unsaturated aldehyde (1 mmol) was added and reflux was continued for further 30 min. After completion of the reaction, as judged by TLC, it was cooled and diluted with dichloromethane (20 mL), and washed with water (5 mL). The organic layer was separated and dried over sodium sulfate. Solvents were evaporated under reduced pressure and the crude residue was purified by chromatography on silica gel (petroleum ether-ethyl acetate 80:20 to 90-10, v/v) as eluent. Characterization data of the compounds isolated are given below.

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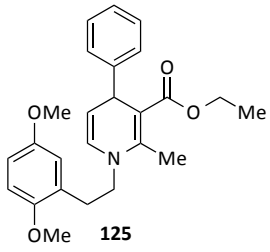
**(±)-Ethyl 1-(2,5-dimethoxyphenethyl)-2-methyl-4-phenyl-1,4-dihydro-pyridine-3-carboxylate (125)**:




**125**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), 3,4-dimethoxyphenylethylamine (181 mg, 1 mmol) and *trans*-cinnamaldehyde (132 mg, 1 mmol), yield: 268 mg (66 %) as a pale brown viscous oil.

Data of **125**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.12 (t, *J* = 7.1 Hz, 3H), 2.52 (s, 3H), 2.89 (t, *J* = 7.7 Hz, 2H), 3,42-3.54 (m, 1H), 3.62-3.77 (m, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 4.00 (q, *J* = 7.1 Hz, 2H), 4.61 (d, *J* = 5.4 Hz, 1H), 4.97 (dd, *J* = 7.6, 5.4 Hz, 1H), 5.97 (d, *J* = 7.6 Hz, 1H), 6.75-6.81 (m, 3H), 7.13-7.20 (m, 1H), 7.25-7.33 (m, 4H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.2, 15.5, 32.2, 40.4, 50.2, 55.8, 59.2, 99.8, 108.2, 111.1, 112.0, 117.1, 126.0, 127.4, 127.5, 128.2, 128.3, 128.6, 148.9, 149.3, 151.9, 153.5, 169.2.

**IR** (NaCl): 2980, 1690, 1490, 1220, 1050 $cm^{-1}$

**Elemental analysis:** Anal. Calcd for $C_{25}H_{29}NO_4$ (M = 407.21): C, 73.68; H, 7.17; N, 3.44**;** Found: C, 73.76; H, 6.90; N, 3.34 %.

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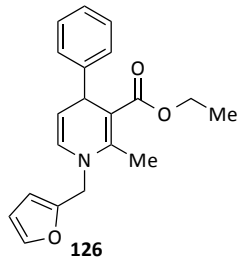
**(±)-Ethyl 1-(furan-2-ylmethyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (126):**



**126**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), furfuryl amine (97 mg, 1 mmol) and *trans*-cinnamaldehyde (132 mg, 1 mmol), yield: 213 mg (66%) as a viscous pale brown oil.

Data of **126**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.12 (t, *J* = 7.1 Hz, 3H), 2.55 (s, 3H), 4.1 (q, *J* = 7.1 Hz, 2H), 4.45-4.55 (m, 3H), 5.00 (dd, *J* = 7.6, 5.5 Hz, 1H), 6.03 (d, *J* = 7.6 Hz, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 6.38 (dd, *J* = 3.1, 2.0 Hz, 1H), 7.13-7.28 (m, 5H), 7.42-7.43 (m, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.2, 15.8, 40.3, 47.0, 59.4, 101.3, 107.8, 108.5, 110.5, 126.0, 127.6, 128.2, 128.7, 142.6, 148.3, 148.8, 151.2, 169.0.

**IR** (NaCl): 2980, 1680, 1570, 1370, 1100 $cm^{-1}$

**Elemental analysis:** Anal. Calcd for $C_{25}H_{29}NO_4$ (M = 323.15): C, 74.28; H, 6.55; N, 4.44**;** Found: C, 73.91; H, 6.24; N, 4.21 %.

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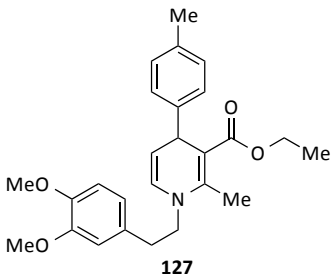
**(±)-Ethyl 1-(3,4-dimethoxyphenethyl)-2-methyl-4-(*p*-tolyl)-1,4-dihydro-pyridine-3-carboxylate (127):**




**127**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), 3,4-dimethoxyphenylethylamine (181 mg, 1 mmol) and trans-(*E*)-3-(*p*-tolyl)acrylaldehyde (146 mg, 1 mmol), yield: 261 mg (62 %) as a pale brown viscous oil.

Data of **127**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.11 (t, *J* = 7.1 Hz, 3H), 2.29 (s, 3H), 2.42 (s, 3H), 2.82 (t, *J* = 7.7 Hz, 2H), 3.42-3.54 (m, 1H), 3.61-3.73 (m, 1H), 3.85-3.86 (m, 6H), 3.93-4.02 (q, *J* = 7.1 Hz, 2H), 4.54 (d, *J* = 5.5 Hz, 1H), 4.92 (dd, *J* = 7.6, 5.5 Hz, 1H), 5.86 (d, *J* = 7.6 Hz, 1H), 6.68-6.82 (m, 3H), 7.05-7.13 (m, 4H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.3, 15.8, 21.1, 36.3, 39.8, 52.0, 56.0, 59.3, 100.2, 108.3, 111.4, 112.0, 120.8, 127.4, 128.5, 129.0, 130.7, 135.5, 146.2, 147.9, 148.2, 149.1, 169.2.

**IR** (NaCl): 2940, 1670, 1510, 1270, 1170, 1100, 1030 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{26}H_{31}NO_4$ (M = 421.23): C, 74.08; H, 7.41; N, 3.32**;** Found: C, 73.96; H, 7.47, N, 3.14 %.

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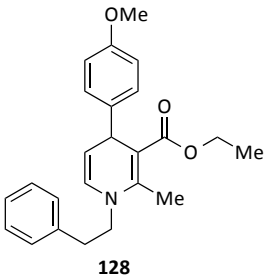
**(±)-Ethyl-4-(4-methoxyphenyl)-2-methyl-1-phenethyl-1,4-dihydro-pyridine-3-carboxylate (128):**




**128**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), phenylethylamine (121 mg, 1 mmol) and (*E*)-3-(4-methoxyphenyl) acrylaldehyde (162 mg, 1 mmol), yield: 256 mg (68 %) as an orange solid.

Data of **128**.

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.26 (t, *J* = 7.1 Hz, 3H), 2.56 (s, 3H), 3.02 (t, *J* = 7.5 Hz, 2H), 3.57-3.69 (m, 1H), 3.78-3.87 (m, 1H), 3.92 (s, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.67 (d, *J* = 5.4 Hz, 1H), 5.07 (dd, *J* = 7.6, 5.5 Hz, 1H), 6.03 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.26-7.35 (m, 4H), 7.39-7.49 (m, 3H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.3, 15.8, 36.8, 39.3, 52.0, 55.3, 59.3, 100.5, 108.4, 113.6, 126.8, 128.4, 128.5, 128.8, 128.9, 138.1, 141.6, 148.1, 157.9, 169.2.

**IR** (NaCl): 2940, 2800, 1730, 1600, 1520, 1350, 1180 $cm^{-1}$

**Elemental analysis:** Anal. Calcd for $C_{24}H_{27}NO_3$ (M = 377.20): C, 76.36; H, 7.21; N, 3.71; Found: C, 75.91; H, 7.01; N, 3.95 %.

**MP:** 80-81 °C

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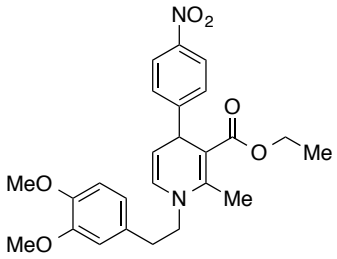
**(±)-Ethyl-1-(3,4-dimethoxyphenethyl)-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (130):**




**130**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), 3,4-dimethoxyphenylethylamine (181 mg, 1 mmol) and (*E*)-3-(4-nitrophenyl) acrylaldehyde (177 mg, 1 mmol), yield: 352 mg (78 %) as a pale brown solid.

Data of **130**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.07 (t, *J* = 7.1 Hz, 3H), 2.45 (s, 3H), 2.83 (t, *J* = 7.1 Hz, 2H), 3.47-3.59 (m, 1H), 3.64-3.76 (m, 1H), 3.86-3.88 (m, 6H), 3.97 (q, *J* = 7.1 Hz, 2H), 4.70 (d, *J* = 5.3 Hz, 1H), 4.83-4.90 (m, 1H), 5.90 (d, *J* = 7.6 Hz, 1H), 6.68-6.82 (m, 3H), 7.34 (dd, *J* = 8.7, 2.0 Hz, 2H), 8.12 (dd, *J* = 8.6, 2.1 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.3, 15.8, 36.2, 40.6, 52.0, 56.0, 56.1, 59.6, 98.8, 106.7, 111.4, 112.0, 120.9, 123.7, 128.2, 129.5, 130.2, 146.3, 148.0, 149.2, 149.5, 156.2, 168.5.

**IR** (NaCl): 2920, 1670, 1590, 1500, 1340, 1260, 1020 $cm^{-1}$

**Elemental analysis:** Anal. Calcd for $C_{25}H_{28}N_2O_6$ (M = 452.19): C, 66.36; H, 6.24; N, 6.19; Found: C, 66.06; H, 5.91; N, 5.83 %.

**MP:** 76-77 °C.

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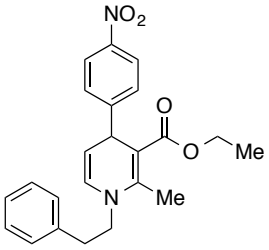
**(±)-Ethyl-2-methyl-4-(4-nitrophenyl)-1-phenethyl-1,4-dihydropyridine-3-carboxylate (132):**




**132**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), phenylethylamine (121 mg, 1 mmol) and (*E*)-3-(4-nitrophenyl)acrylaldehyde (177 mg, 1 mmol), yield: 337 mg (86 %) as a viscous pale brown oil.

Data of **132**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.23 (t, *J* = 7.1 Hz, 3H), 2.59 (s, 3H), 3.02 (t, *J* = 6.6 Hz, 2H), 3.61-3.74 (m, 1H), 3.82-3.91 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 4.84 (d, *J* = 4.9 Hz, 1H), 4.98-5.03 (m, 1H), 6.03-6.07 (m, 1H), 7.31-7.50 (m, 7H), 8.25-8.29 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.3, 15.8, 36.7, 40.6, 51.9, 59.9, 98.7, 106.8, 123.7, 127.0, 128.2, 128.9, 129.4, 137.7, 146.3, 149.6, 156.2, 168.5 (one quaternary carbon is merged with others in the aromatic region).

**IR** (NaCl): 2920, 1670, 1510, 1350, 1170, 1100 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{23}H_{24}N_2O_4$ (M = 392.17): C, 70.39; H, 6.16; N, 7.14. Found: C, 69.97; H, 6.07; N, 6.97 %.

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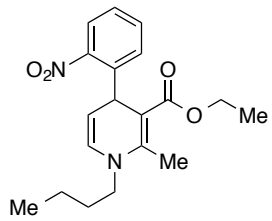
**(±)-Ethyl 1-butyl-2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (133):**



Prepared from ethyl acetoacetate (130 mg, 1 mmol), butylamine (73 mg, 1 mmol) and (*E*)-3-(4-nitrophenyl) acrylaldehyde (177 mg, 1 mmol), yield: 233 mg (68 %) as a viscous pale brown oil.

Data of **133**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.89-1.02 (m, 6H), 1.35-1.44 (m, 2H), 1.35-1.44 (m, 2H), 2.54 (s, 3H), 3.23-3.35 (m, 1H), 3.42-3.55 (m, 1H), 3.86 (q, *J* = 7.0 Hz, 2H), 5.08 (d, *J* = 5.1 Hz, 1H), 5.16 (dd, *J* = 7.5, 5.1 Hz, 1H), 5.91 (d, *J* = 7.6 Hz, 1H), 7.24-7.31 (m, 1H), 7.55 (d, *J* = 3.9 Hz, 2H), 7.72 (d, *J* = 7.9 Hz, 1H)

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 13.9, 15.5, 20.0, 32.4, 36.3, 50.3, 58.5, 59.3, 98.6, 106.8, 123.1, 126.5, 129.5, 131.2, 133.1, 144.0, 147.6, 150.6, 168.2.

**IR** (NaCl): 2940, 1660, 1520, 1350, 1180, 1080, 750 $cm^{-1}$

**Elemental analysis:** Anal. Calcd for $C_{19}H_{24}N_2O_4$ (M = 344.17): C, 66.26; H, 7.02; N, 8.13. Found: C, 65.85; H, 6.82; N, 8.21 %.

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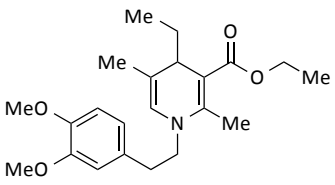
**(±)-Ethyl-1-(3,4-dimethoxyphenethyl)-4-ethyl-2,5-dimethyl-1,4-dihydro-pyridine-3-carboxylate (134):**



**134**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), 3,4-dimethoxyphenylethylamine (181 mg, 1 mmol) and (*E*)-2-methylpent-2-enal (98 mg, 1 mmol), yield: 238 mg (64 %) as a viscous pale brown oil.

Data of **134**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.78 (t, *J* = 7.3 Hz, 3H), 1.21-1.29 (m, 6H), 2.37 (s, 3H), 2.69-2.80 (m, 2H), 3.27-3.44 (m, 2H), 3.57-3.76 (m, 2H), 3.84-3.87 (m, 7H), 4.11 (q, *J* = 7.1 Hz, 2H), 5.74 (s, 1H), 6.66-6.82 (m, 3H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 9.48, 14.6, 15.5, 18.9, 27.2, 36.3, 39.1, 51.8, 56.0, 56.1, 59.1, 97.0, 111.4, 112.0, 115.7, 120.7, 125.4, 130.9, 147.8, 149.0, 149.1, 169.6.

**IR** (NaCl): 2940, 1600, 1510, 1260, 1150, 1030 $cm^{-1}$

**Elemental analysis:** Anal. Calcd for $C_{22}H_{31}NO_4$ (M = 373.23): C, 70.75; H, 8.37; N, 3.75. Found: C, 70.70; H, 8.53; N, 4.00 %.

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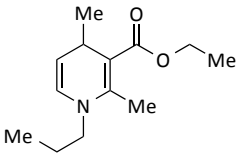
**(±)-Ethyl-2,4-dimethyl-1-propyl-1,4-dihydropyridine-3-carboxylate (136):**




**136**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), propyl amine (59 mg, 1 mmol) and (*E*)-but-2-enal (70 mg, 1 mmol), yield: 151 mg (68 %) as a viscous pale brown oil.

Data of **136**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.87-0.96 (m, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.51-1.60 (m, 2H), 2.35 (s, 3H), 3.05-3.16 (m, 1H), 3.26-3.47 (m, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.84 (dd, *J* = 7.4, 5.9 Hz, 1H), 5.79 (d, *J* = 7.4 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 11.2, 14.6, 15.8, 23.7, 25.0, 28.3, 51.8, 59.2, 100.8, 108.9, 129.4, 149.0, 169.5.

**IR** (NaCl): 2940, 1660, 1560, 1230, 1090 $cm^{-1}$

**Elemental analysis:** Anal. Calcd for $C_{13}H_{21}NO_2$ (M = 223.31): C, 69.92; H, 9.48; N, 6.27; Found: C, 69.73; H, 9.22; N, 5.97 %.

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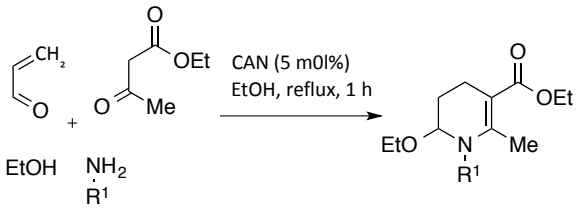
### 7.5.2: Synthesis of tetrahydropyridine (THP) derivatives.




A stirred solution of the requisite primary amine (1 mmol), ethyl acetoacetate (1 mmol) and the CAN catalyst (5 mol%) in acetonitrile (3 mL) was stirred for 30 min at room temperature. Acrolein (1 mmol, 1 equiv) and ethanol (2 mmol) were then added and the mixture was stirred for a further 30 min. After completion of the reaction, as monitored by TLC, the mixture was diluted with ethyl acetate (20 mL) and washed with water (5 mL). The organic phase was dried (anhydrous $Na_2SO_4$) and the solvent was removed by rotavapor below 25 °C. The residue was purified by flash column chromatography on neutral alumina, eluting with a petroleum ether/ethyl acetate mixture (90:10, v/v). Compounds **139**-**141** were known in the literature,[134a] and **143** and **144** had to be used in crude state beacause all attempts at their purification led to their decomposition.

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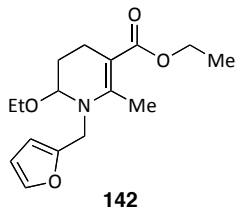
**Ethyl 6-ethoxy-1-(furan-2-ylmethyl)-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (142):**




**142**

Prepared from ethyl acetoacetate (130 mg, 1 mmol), furfuryl amine (97 mg, 1 mmol) and acrolein (56 mg, 1 mmol), yield: 190 mg (65 %) as a brown solid.

Data of **142**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.19-1.21 (m, 6H), 1.42

(tdd, *J* = 13.5, 5.5, 2.5 Hz, 1H), 1.95-2.05 (m, 1H), 2.30 (tdd, *J* = 13.5, 4.9, 1.6 Hz, 1H), 2.45-2.54 (m, 4H), 3.42-3.56 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.34 (d, *J* = 17.1 Hz, 1H), 4.52 (brs, 1H), 4.65 (d, *J* = 17.1 Hz, 1H), 6.14 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.9 Hz, 1H), 7.34 (dd, *J* = 1.8, 0.8 Hz, 1H).

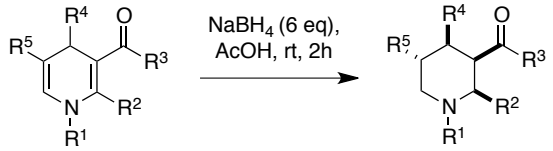
**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.7, 15.6, 16.6, 18.1, 25.0, 46.1, 59.1, 62.3, 86.0, 98.0, 107.3, 110.3, 142.3, 151.3, 152.1, 169.1.

**IR** (NaCl): 3300, 2980, 1680, 1430, 1370, 1240, 1020 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{16}H_{23}NO_4$ (M = 293.16): C, 65.51; H, 7.90; N, 4.77; Found: C, 65.22; H, 7.55; N, 5.02 %.

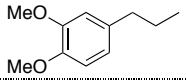
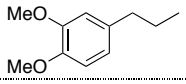
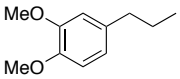
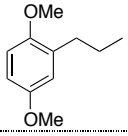
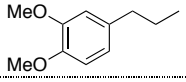
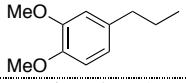
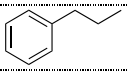
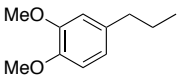
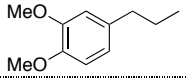
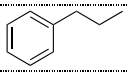
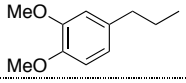
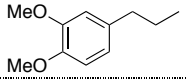
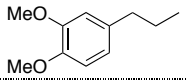
**MP:** 80-81 °C.

## 7.5.3. Synthesis of polysubstituted piperidine derivatives through the STAB reduction of dihydropyridines

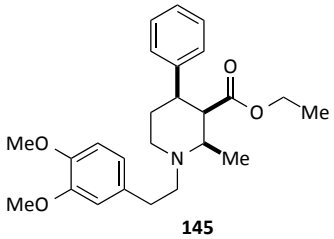



**145-164**

To stirred glacial acetic acid (3 mL) was added sodium borohydride (6 mmol) in three portions, keeping the temperature of the solvent between 15 and 20 °C, in order to prepare sodium triacetoxyborohydride ($NaBH_4(OAc)_3$). After hydrogen evolution had ceased (10 min), the requisite substituted dihydropyridine (1 mmol) was added in one portion and the reaction mixture was stirred for 2 h. After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with water (10 mL), neutralized with saturated sodium hydrogen carbonate solution, and extracted twice with dichloromethane (20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude products were purified by flash column chromatography on neautral alumina, eluting with petroleum ether/ethyl acetate (gradient from 70:30 to 80:20, v/v). Characterization data for the obtained piperidine derivatives are given below.

| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| **145** |  | Me | OEt | Ph | H |
| **146** |  | *n*-Pr | OEt | Ph | H |
| **147** |  | Me | O-$^t$Bu | Ph | H |
| **148** |  | Me | OEt | Ph | H |
| **149** |  | Me | OEt | Ph | H |
| **150** |  | Me | OEt | *p*-$MeC_6H_4$ | H |
| **151** |  | Me | OEt | *p*-$MeOC_6H_4$ | H |
| **152** |  | Me | OEt | *p*-$MeOC_6H_4$ | H |
| **153** |  | Me | OEt | *p*-$ClC_6H_4$ | H |
| **154** | Bn | Me | OEt | *p*-$NO_2C_6H_4$ | H |
| **155** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H |
| **156** |  | Me | OEt | *p*-$NO_2C_6H_4$ | H |
| **157** | *n*-Pr | Me | O-$^t$Bu | *p*-$NO_2C_6H_4$ | H |
| **158** | *n*-Bu | Me | OEt | *o*-$NO_2C_6H_4$ | H |
| **159** |  | Me | OEt | Et | Me |
| **160** |  | Me | OEt | Me | H |
| **161** | Bn | Me | OEt | Me | H |
| **162** |  | Me | OEt | H | Me |
| **163** | *n*-Pr | Me | OEt | Me | H |
| **164** | *n*-Bu | Me | OEt | Me | H |

**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-(3,4-dimethoxyphenethyl)-2-methyl-4-phenyl-piperidine-3-carboxylate (145):**




**145**

Prepared from compound **105** (122 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 108 mg (88 %) as a viscous pale brown oil.

Data of **145**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.93 (t, *J* = 7.1 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.74 (d, *J* = 9.0 Hz, 1H), 2.50-2.58 (m, 1H), 2.71-2.88 (m, 7H), 2.94-3.01 (m, 1H), 3.30 (d, *J* = 11.1 Hz, 1H), 3.80-3.93 (m, 8H), 6.75-6.85 (m, 3H), 7.19-7.34 (m, 5H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.1, 18.6, 25.7, 29.9, 44.6, 53.1, 53.6, 55.6, 55.9, 56.0, 57.3, 59.4, 111.3, 112.1, 120.5, 126.5, 127.4, 128.2, 133.6, 142.8, 147.3, 148.8, 171.3.

**IR** (NaCl): 2940, 1730, 1590, 1510, 1460, 1270, 1030 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{25}H_{33}NO_4$ (M = 411.24): C, 72.96; H, 8.08; N, 3.40; Found: C, 72.62; H, 7.82; N, 3.49 %.

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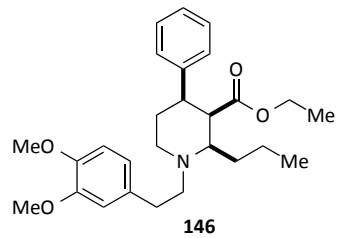
**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-(3,4-dimethoxyphenylethyl)-4-phenyl-2-propyl-piperidine-3-carboxylate (146):**




**146**

Prepared from compound **115** (130 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 104 mg (79 %) as a viscous pale pink oil.

Data of **146**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.87-1.04 (m, 6H), 1.27-1.43 (m, 2H), 1.55-1.84 (m, 3H), 2.60-3.10 (m, 8H), 3.32 (d, *J* = 11.4 Hz, 1H), 3.73-3.91 (m, 9H), 6.74-6.84 (m, 3H), 7.20-7.42 (m, 5H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.0, 14.5, 19.5, 24.6, 30.9, 33.6, 44.7, 49.8, 53.2, 54.2, 55.8, 55.9, 59.3, 62.3, 111.2, 112.0, 120.5, 126.5, 127.4, 128.2, 133.5, 142.9, 147.2, 148.8, 171.5.

**IR** (NaCl): 2940, 1720, 1510, 1460, 1150, 1030 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{27}H_{37}NO_4$ (M = 439.27): C, 73.77; H, 8.48; N, 3.19. Found: C, 73.95; H, 8.73; N, 3.13 %.

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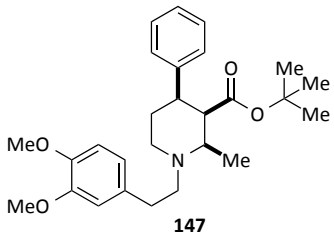
**(±)-(2*S**,3*S**,4*R**)-*tert*-Butyl 1-(3,4-dimethoxyphenethyl)-2-methyl-4-phenylpiperidine-3-carboxylate (147):**




**147**

Prepared from compound **80** (130 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid**,** yield: 111 mg (84 %) as a viscous orange.

Data of **147**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.08-1.36 (m, 13H), 1.46-.52 (m, 1H), 1.76 (d, *J* = 10.7 Hz, 1H), 2.76-3.06 (m, 7H), 3.32 (d, *J* = 11.0 Hz, 1H), 3.83-3.93 (m, 6H), 6.76-6.85 (m, 3H), 7.22-7.34 (m, 5H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 18.2, 25.1, 27.8, 29.9, 44.1, 52.9, 53.5, 55.9, 56.0, 57.4, 79.9, 111.4, 112.1, 120.6, 126.4, 127.6, 128.1, 128.8, 133.3, 142.5, 147.3, 148.9, 170.7.

**IR** (NaCl): 2920, 1720, 1510, 1450, 1260, 1150, 1030 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{27}H_{37}NO_4$ (M = 439.27): C, 73.77; H, 8.48; N, 3.19; Found: C, 73.48; H, 8.23; N, 2.94 %.

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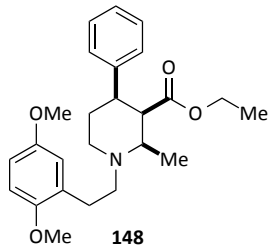
**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-(2,5-dimethoxyphenethyl)-2-methyl-4-phenyl-piperidine-3-carboxylate (148):**




**148**

Prepared from compound **125** (122 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 96 mg (78 %) as a viscous pale pink oil.

Data of **148**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.94 (t, *J* = 7.1 Hz, 3H), 1.24-1.32 (m, 5H), 1.75 (d, *J* = 7.7 Hz, H), 2.69-3.00 (m, 7H), 3.27 (d, *J* = 10.5 Hz, 1H), 3.80-3.94 (m, 8H), 6.71-6.81 (m, 3H), 7.21-7.34 (m, 5H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.1, 18.3, 23.8, 25.9, 44.7, 53.0, 53.7, 55.8, 55.9, 56.6, 59.4, 110.9, 111.2, 116.8, 126.5, 127.5, 127.6, 128.3, 128.4, 143.0, 151.9, 153.5, 171.4.

**IR** (NaCl): 2920, 1720, 1490, 1450, 1220, 1150, 1030 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{25}H_{33}NO_4$ (M = 411.24): C, 72.96; H, 8.08; N, 3.40; Found: C, 72.58; H, 7.78; N, 3.46 %.

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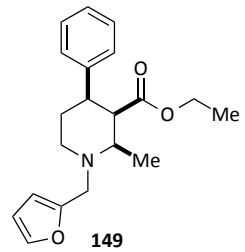
**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-(furan-2-ylmethyl)-2-methyl-4-phenyl-piperidine-3-carboxylate (149):**




**149**

Prepared from compound 126 (98 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 90 mg (92 %) as a viscous pale brown oil.

Data of **149**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.93 (t, *J* = 7.0 Hz, 3H), 1.35 (d, *J* = 6.5 Hz, 3H), 1.67-1.71 (m, 1H), 2.42-2.52 (m, 1H), 2.60-2.67 (m, 1H), 2.76-2.89 (m, 3H), 3.14-3.20 (m, 1H), 3.79-3.93 (m, 3H), 4.08 (d, *J* = 15.6 Hz, 1H), 6.23 (d, *J* = 3.0 Hz, 1H), 6.37 (dd, *J* = 3.0, 1.9 Hz, 1H), 7.18-7.42 (m, 6H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 13.8, 15.6, 25.2, 35.5, 48.3, 52.4, 54.0, 55.1, 60.9, 110.3, 110.6, 125.0, 128.3, 128.7, 137.2, 141.8, 148.3, 171.0

**IR** (NaCl): 2920, 1720, 1450, 1180, 1150, 1020 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{20}H_{25}NO_3$ (M = 327.18): C, 73.37; H, 7.70; N, 4.28; Found: C, 73.56; H, 7.42; N, 4.24 %.

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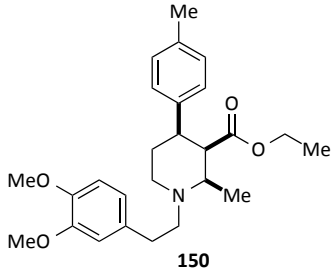
**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-(3,4-dimethoxyphenethyl)-2-methyl-4-(*p*-tolyl)-piperidine-3-carboxylate (150):**




**150**

Prepared from compound **127** (126 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 99 mg (78 %) as a brown solid.

Data of **150**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.93 (t, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.69 (d, *J* = 7.7 Hz, 1H), 1.85-2.06 (m, 2H), 2.30 (s, 3H), 2.44-2.54 (m, 1H), 2.69-2.82 (m, 6H), 3.23-3.28 (m, 1H), 3.82-3.88 (m, 8H), 6.72-6.81 (m, 3H), 7.05-7.14 (m, 4H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.2, 18.7, 26.0, 29.8, 44.3, 53.3, 53.7, 55.7, 55.9, 56.0, 57.4, 59.4, 111.3, 112.1, 120.6, 127.3, 128.9, 133.7, 135.9, 139.9, 147.2, 148.9, 171.4.

**IR** (NaCl): 2920, 1710, 1500, 1260, 1140, 1020 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{26}H_{35}NO_4$ (M = 425.26): C, 73.38; H, 8.29; N, 3.29; Found: C, 73.10; H,7.95; N, 3.15%.

**MP:** 82-83 °C.

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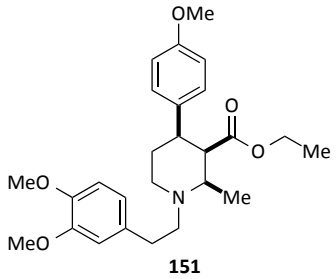
**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-(3,4-dimethoxyphenethyl)-4-(4-methoxyphenyl)-2-methylpiperidine-3-carboxylate (151):**




**151**

Prepared from compound **82** (131 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 94 mg (71 %) as a viscous pale pink oil.

Data of **151**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.95 (t, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.67 (d, *J* = 7.5 Hz, 1H), 2.45-2.53 (m, 1H), 2.69-2.80 (m, 6H), 2.92-3.02 (m, 1H), 3.23-3.28 (m, 1H), 3.77-3.88 (m, 12H), 6.71-6.83 (m, 5H), 7.13-7.17 (d, *J* = 8.7 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.2, 18.7, 26.2, 29.8, 43.8, 53.3, 53.8, 55.3, 55.7, 55.9, 56.03, 57.3, 59.4, 111.3, 112.1, 113.6, 120.6, 128.4, 133.7, 135.1, 147.3, 148.9, 158.2, 171.5.

**IR** (NaCl): 2920, 1740, 1600, 1500, 1450, 1250, 1140, 1000 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{26}H_{35}NO_4$ (M = 441.25): C, 70.72; H, 7.99; N, 3.17; Found: C, 70.45; H, 7.62; N, 3.22 %.

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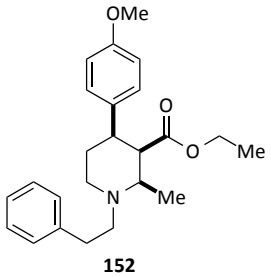
**(±)-(2*S**,3*S**,4*R**)-Ethyl 4-(4-methoxyphenyl)-2-methyl-1-phenylethyl-piperidine-3-carboxylate (152):**




**152**

Prepared from compound **128** (113 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 78 mg (68 %) as a viscous pale pink oil.

Data of **152**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.10 (t, *J* = 7.1 Hz, 3H),

1.35 (d, *J* = 6.3 Hz, 3H), 1.77-1.84 (m, 1H), 2.60-2.72 (m, 1H), 2.82-3.18 (m, 8H), 3.37-3.43 (m, 1H), 3.90-4.08 (m, 5H), 6.94-6.99 (m, 2H), 7.24-7.46 (m, 7H).

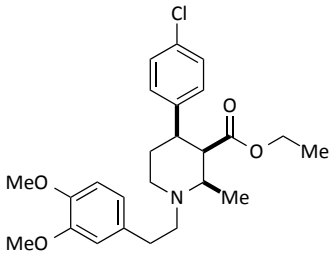
**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.2, 18.6, 26.2, 29.9, 43.8, 53.2, 53.8, 55.3, 55.6, 57.0, 59.4, 113.6, 125.9, 128.4, 128.5, 128.8, 135.1, 141.0, 158.2, 171.5.

**IR** (NaCl): 2940, 1720, 1610, 1510, 1250, 1040 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{24}H_{31}NO_3$ (M = 381.23): C, 75.56; H, 8.19; N, 3.67; Found: C, 75.42; H, 8.21; N, 3.75 %.

---

**(±)-(2*S**,3*S**,4*R**)-Ethyl 4-(4-chlorophenyl)-1-(3,4-dimethoxyphenethyl)-2-methylpiperidine-3-carboxylate (153):**




**153**

Prepared from compound **81** (132 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 120 mg (90 %) as an orange solid.

Data of **153**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.98 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.68-1.78 (m, 1H), 2.48-2.56 (m, 1H), 2.63-2.92 (m, 7H), 2.95-3.05 (m, 1H), 3.26-3.32 (m, 1H), 3.80-3.96 (m, 8H), 6.74-6.84 (m, 3H), 7.17-7.29 (m, 4H).

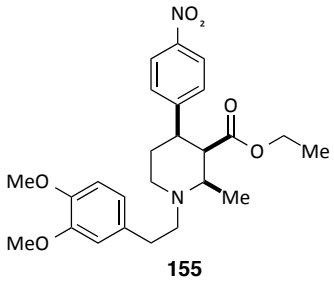
**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.1, 18.6, 25.7, 29.9, 43.9, 53.0, 53.3, 55.5, 55.9, 56.0, 57.3, 59.5, 111.2, 112.0, 120.5, 128.3, 128.8, 132.1, 133.4, 141.3, 147.2, 148.8, 171.1.

**IR** (NaCl): 2940, 1730, 1510, 1270, 1160, 1030 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{25}H_{32}ClNO_4$ (M = 445.20): C, 67.33; H, 7.23; N, 3.14; Found: C, 66.98; H, 7.08; N, 3.26 %.

**MP:** 65-66 °C.

**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-(3,4-dimethoxyphenylethyl)-2-methyl-4-(4-nitrophenyl)piperidine-3-carboxylate (155):**




**155**

Prepared from compound **130** (135 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 119 mg (87 %) as a brown solid.

Data of **155**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.94 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.75 (m, 1H), 2.52 (t, *J* = 11.5 Hz, 1H), 2.69-2.97 (m, 8H), 3.29 (d, *J* = 11.1 Hz, 1H), 3.76-3.94 (m, 8H), 6.73-6.82 (m, 3H), 7.41 (d, *J* = 8.2 Hz, 2H), 8.14 (d, *J* = 7.3 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.2, 18.7, 25.6, 30.1, 44.5, 52.9, 53.0, 55.4, 55.9, 56.0, 57.6, 59.8, 111.3, 112.1, 120.6, 123.6, 128.4, 133.4, 146.7, 147.3, 148.9, 150.5, 170.8.

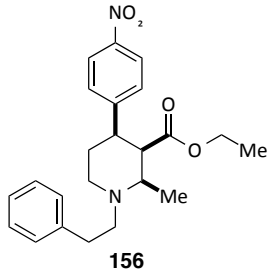
**IR** (NaCl): 2940, 1730, 1600, 1510, 1350, 1160, 1030 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{25}H_{32}N_2O_6$ (M = 456.23): C, 65.77; H, 7.07; N, 6.14: Found: C, 65.51; H, 7.00; N, 6.05 %.

**MP:** 93-94 °C.

---

**(±)-(2*S**,3*S**,4*R**)-Ethyl 2-methyl-4-(4-nitrophenyl)-1-phenylethyl-piperidine-3-carboxylate (156):**




**156**

Prepared from compound **132** (117 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 103 mg (86 %) as a viscous pale brown oil.

Data of **156**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.10 (t, *J* = 7.1 Hz, 3H), 1.38 (d, *J* = 6.3 Hz, 3H), 1.89 (m, 1H), 2.65-2.74 (m, 1H), 2.84-3.19 (m, 8H),

3.40-3.46 (m, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 7.31-7.36 (m, 3H), 7.40-7.47 (m, 2H), 7.54-7.57 (m, 2H), 8.26-8.31 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.2, 18.6, 25.6, 30.1, 44.5, 52.8, 53.0, 55.3, 57.4, 59.8, 123.5, 126.0, 128.5, 128.6, 128.8, 140.8, 146.7, 150.6, 170.8.

**IR** (NaCl): 2940, 1600, 1530, 1440, 1180, 1100 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{23}H_{28}N_2O_4$ (M = 396.20): C, 69.67; H, 7.12; N, 7.07; Found: C, 70.07; H, 6.88; N, 6.76 %.

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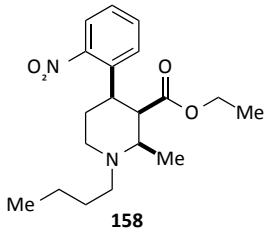
**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-butyl-2-methyl-4-(2-nitrophenyl)piperidine-3-carboxylate (158):**




**158**

Prepared from compound **133** (103 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 82 mg (79 %) as a viscous pale brown oil.

Data of **158**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.88-0.96 (m, 6H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.21-1.33 (m, 2H), 1.35-1.56 (m, 3H), 2.36 (td, *J* = 11.6, 2.5 Hz, 1H), 2.45-2.91 (m, 4H), 2.95-2.98 (m, 1H), 3.14 (dt, *J* = 11.2, 3.1 Hz, 1H), 3.37 (dt, *J* = 12.9, 3.8 Hz, 1H), 3.84 (q, *J* = 7.1 Hz, 2H), 7.30-7.36 (m, 1H), 7.50 (d, *J* = 3.9 Hz, 2H), 7.80 (d, *J* = 7.9 Hz, 1H).

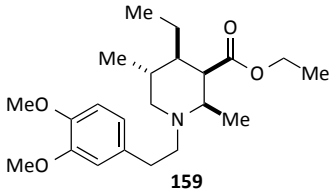
**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.2, 18.5, 20.9, 25.3, 26.6, 40.0, 51.7, 52.8, 53.2, 57.3, 59.5, 124.5, 127.4, 129.6, 132.7, 137.2, 149.9, 171.3 (two aliphatic carbons are merged)

**IR** (NaCl): 2940, 1620, 1520, 1350, 1160, 1030 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{20}H_{28}N_2O_4$ (M = 348.20): C, 65.49; H, 8.10; N, 8.04; Found: C, 65.43; H, 7.86; N, 8.12 %.

---

**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-(3,4-dimethoxyphenylethyl)-4-ethyl-2,5-dimethylpiperidine-3-carboxylate (159):**




**159**

Prepared from compound **134** (111 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 70 mg (62 %) as a viscous yellow oil.

Data of **159**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.83-1.05 (m, 9H), 1.17-1.29 (m, 6H), 1.63-1.72 (m, 1H), 1.94-2.04 (m, 1H), 2.23-2.42 (m, 1H), 2.50-2.75 (m, 4H), 2.83-2.98 (m, 2H), 3.84-3.87 (m, 6H), 4.12 (q, *J* = 7.1 Hz, 2H), 6.68-6.79 (m, 3H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 11.9, 14.5, 17.5, 18.4, 22.8, 29.5, 31.3, 47.5, 49.5, 55.7, 55.9, 56.0, 57.5, 59.5, 61.2, 111.3, 112.1, 120.5, 133.7, 147.2, 148.8, 172.3.

**IR** (NaCl): 2940, 1570, 1360, 1300, 1090 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{22}H_{35}NO_4$ (M = 377.26): C, 69.99; H, 9.34; N, 3.71; Found: C, 69.59; H, 9.05; N, 3.82 %.

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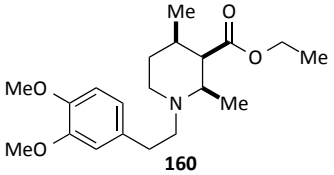
**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-(3,4-dimethoxyphenylethyl)-2,4-dimethyl-piperidine-3-carboxylate (160):**




**160**

Prepared from compound **83** (103 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 79 mg (75 %) as a viscous orange oil.

Data of **160**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.96 (d, *J* = 6.8 Hz, 3H), 1.15-1.27 (m, 6H), 1.41 (dd, *J* = 12.4, 2.8 Hz, 1H), 1.65-1.76 (m, 1H), 1.98-2.15 (m, 1H), 2.36 (td, *J* =

11.8, 2.5 Hz, 1H), 2.49-2.78 (m, 5H), 2.84-2.95 (m, 1H), 3.04 (dt, *J* = 11.2, 3.4 Hz, 1H), 3.84-3.86 (m, 6H), 4.14 (q, *J* = 7.1 Hz, 2H), 6.68-6.79 (m, 3H)

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.6, 18.2, 19.1, 29.6, 29.8, 33.6, 52.4, 52.6, 55.7, 55.9, 56.0, 56.7, 59.5, 111.2, 112.1, 120.5, 133.7, 147.2, 148.8, 172.2.

**IR** (NaCl): 2920, 1720, 1510, 1450, 1260, 1150, 1030 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{20}H_{31}NO_4$ (M = 349.23): C, 68.74; H, 8.94; N, 4.01; Found: C, 68.72; H, 8.46; N, 4.15 %.

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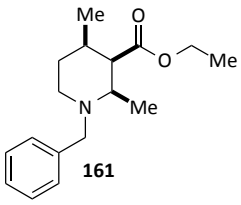
**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-benzyl-2,4-dimethylpiperidine-3-carboxylate (161):**




**161**

Prepared from compound **135** (82.5 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 63 mg (77 %) as a viscous pale brown oil.

Data of **161**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.99 (d, *J* = 6.8 Hz, 3H), 1.23-1.37 (m, 8H), 1.71-1.79 (m, 1H), 1.97-2.05 (m, 1H), 2.51-2.58 (m, 2H), 2.89 (dd, *J* = 7.4, 3.0 Hz, 1H), 3.19 (d, *J* = 14.0 Hz, 1H), 4.03-4.26 (m, 3H), 7.22-7.42 (m, 5H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.6, 18.7, 19.2, 29.5, 33.5, 52.9, 53.1, 57.3, 57.9, 59.6, 126.5, 128.3, 128.7, 140.2, 172.3.

**IR** (NaCl): 2950, 1610, 1540, 1460, 1130, 1090 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{17}H_{25}NO_2$ (M = 275.19): C, 74.14; H, 9.15; N, 5.09; Found: C, 73.95; H, 9.05; N, 5.30 %.

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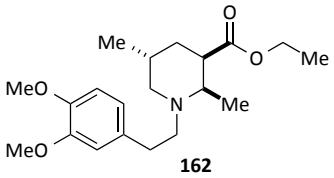
**(±)-(2*S**,3*S**,5*R**)-Ethyl 1-(3,4-dimethoxyphenethyl)-2,5-dimethyl-piperidine-3-carboxylate (162):**




**162**

Prepared from compound **138** (103 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 75 mg (67 %) as a viscous yellow oil.

Data of **162**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.96-1.02 (m, 6H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.38 (dt, *J* = 13.4, 4.9 Hz, 1H), 1.87 (m, 1H), 2.02-2.06 (m, 1H), 2.21 (dd, *J* = 11.1, 4.6 Hz, 1H), 2.66-2.74 (m, 5H), 2.81-2.85 (m, 1H), 3.11-3.13 (m, 1H), 3.85-3.87 (m, 6H), 4.12 (q, *J* = 7.1 Hz, 2H), 6.70-6.80 (m, 3H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.3, 18.8, 27.3, 29.6, 32.6, 43.1, 53.8, 55.3, 55.8, 55.9, 56.6, 60.0, 111.1, 112.0, 120.5, 133.6, 147.1, 148.6, 174.0.

**IR** (NaCl): 2940, 2820, 1720, 1590, 1450, 1260, 1040 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{19}H_{31}NO_4$ (M = 349.23): C, 68.74; H, 8.94; N, 4.01; Found: C, 68.52; H, 8.61; N, 4.12 %.

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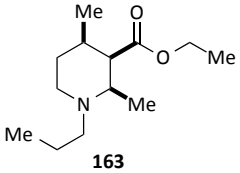
**(±)-(2*S**,3*S**,4*R**)-Ethyl 2,4-dimethyl-1-propylpiperidine-3-carboxylate (163):**




**163**

Prepared from compound **136** (66 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 46 mg (72 %) as a viscous pale brown oil.

Data of **163**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.79-0.95 (m, 6H), 1.11 (d, *J* = 6.2 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.33-1.48 (m, 3H), 1.61-1.71 (m, 1H), 1.88-2.10 (m, 1H), 2.16-2.25 (m, 1H), 2.34-2.66 (m, 4H), 2.94 (dt, *J* = 11.2, 3.5 Hz, 1H), 4.13 (q, *J* = 7.0 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 12.1, 14.6, 16.7, 19.1, 29.6, 29.8, 33.5, 52.3, 52.4, 55.5, 56.8, 59.5, 172.4.

**IR** (NaCl): 3240, 2920, 1720, 1580, 1470, 1240, 1090 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{13}H_{25}NO_2$ (M = ): C, 68.68; H, 11.08; N, 6.16; Found: C, 68.52; H, 10.80; N, 6.21 %.

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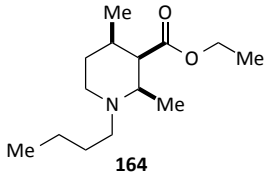
**(±)-(2*S**,3*S**,4*R**)-Ethyl 1-butyl-2,4-dimethylpiperidine-3-carboxylate (164):**




**164**

Prepared from compound **137** (71 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 56 mg (76 %) as a viscous pale brown oil.

Data of **164**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.85-0.95 (m, 6H), 1.10-1.43 (m, 11H), 1.59-1.72 (m, 1H), 1.93-2.09 (m, 1H), 2.16-2.27 (m, 1H), 2.33-2.48 (m, 3H), 2.59-2.70 (m, 1H), 2.90-2.97 (dt, *J* = 11.2, 3.5 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.2, 14.6, 18.0, 19.1, 20.9, 25.6, 29.6, 33.5, 52.3, 52.5, 53.2, 56.8, 59.5, 172.4**.**

**IR** (NaCl): 3400, 2900, 1720, 1670, 1560, 1450, 1370, 1140 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{14}H_{27}NO_2$ (M = 241.20): C, 69.66; H, 11.27; N, 5.80; Found: C, 69.88; H, 11.23; N, 5.52 %.

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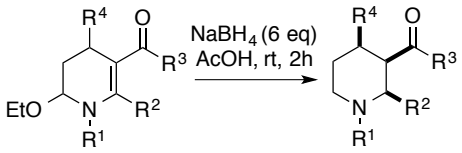
### 7.5.3: Reduction of 6-alkoxy-1,4,5,6-tetrahydropyridines with STAB.

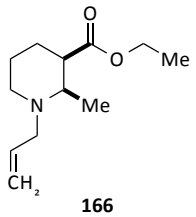



**166-171**

| Compds | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **166** | $CH_2$-CH=$CH_2$ | H | H |
| **167** | $CH_2$-C≡CH | H | H |
| **168** |  | H | Me |
| **169** |  | Et | Me |
| **170** |  | H | H |
| **171** | *n*-Bu | H | H |

To stirred glacial acetic acid (3 mL), sodium borohydride (6 mmol) was added in three portions, keeping the temperature between 15 and 20 °C, to prepare sodium triacetoxyborohydride ($NaBH_4(OAc)_3$). After hydrogen evolution had ceased (10 min), the requisite tetrahydropyridine (1 mmol) was added in one portion and the reaction mixture was stirred for 2 h. After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with water (10 mL), neutralized with saturated sodium hydrogen carbonate solution, and extracted twice with dichloromethane (20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude products were purified by flash column chromatography on neutral alumina, eluting with petroleum ether/ethyl acetate (gradient from 70:30 to 75:25, v/v). Spectral data for the obtained piperidines are given below.

**(±)-(2*S**,3*S**)-Ethyl-1-allyl-2-methylpiperidine-3-carboxylate (166):**



**166**

Prepared from compound **140** (62 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 49 mg (78 %) as a viscous pale brown oil.

Data of **166**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.85 (d, *J* = 6.6 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.43-1.81 (m, 4H), 2.36 (td, *J* = 11.6, 3.1 Hz, 1H), 2.53-2.58 (m, 1H), 2.74-2.78 (m, 1H), 3.01-3.17 (m, 2H), 3.38-3.48 (m, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 5.10-5.23 (m, 2H), 5.78-5.94 (m, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 5.9, 14.6, 20.8, 24.6, 45.1, 46.3, 53.8, 58.4, 60.5, 117.4, 136.5, 174.3.

**IR** (NaCl): 2920, 2800, 1720, 1370, 1140, 1040 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{12}H_{21}NO_2$ (M = 211.16): C, 67.57; H, 10.87; N, 6.57; Found: C, 67.30; H, 10.46; N, 6.63 %.

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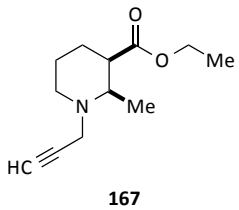
**(±)-(2*R*,3*R*)-Ethyl 2-methyl-1-(prop-2-yn-1-yl)piperidine-3-carboxylate (167):**



**167**

Prepared from compound **141** (61 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 47 mg (75 %) as a viscous pale brown oil.

Data of **167**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.95 (t, *J* = 6.6 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.53-1.82 (m, 4H), 2.20-2.23 (m, 1H), 2.46-2.54 (m, 1H), 2.62-2.74 (m, 2H), 3.24-3.47 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H).

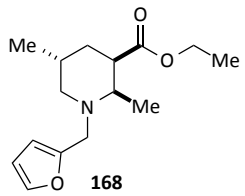
**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 8.5, 14.3, 21.9, 23.9, 44.0, 45.9, 46.9, 54.1, 60.3, 72.7, 79.9, 173.6.

**IR** (NaCl): 3260, 2920, 2800, 1710, 1600, 1440, 1370, 1030 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{12}H_{19}NO_2$ (M = 209.14): C, 68.87; H, 9.15; N, 6.69; Found: C, 68.50; H, 8.80; N, 6.65 %.

---

**(±)-(2*S**,3*S**,5*R**)-Ethyl 1-(furan-2-ylmethyl)-2,5-dimethylpiperidine-3-carboxylate (168):**



**168**

Prepared from compound **144** (78 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 65 mg (82 %) as a viscous pale brown oil.

Data of **168**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.91 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 4H), 1.86-2.12 (m, 3H), 2.70-2.90 (m, 3H), 3.61 (d, *J* = 15.0 Hz, 1H), 3.83 (d, *J* = 15.0 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 6.16 (d, *J* = 3.1 Hz, 1H), 6.31 (dd, *J* = 3.1, 1.9 Hz, 1H), 7.35 (dd, *J* = 1.8, 0.85 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: (one aliphatic carbon merged) 14.5, 19.0, 27.4, 31.8, 44.2, 50.8, 55.3, 56.1, 60.1, 108.4, 110.1, 141.8, 152.7, 174.0.

**IR** (NaCl): 2940, 1730, 1460, 1380, 1150, 1020 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{16}H_{23}NO_3$ (M = 265.17): C, 67.90; H, 8.74; N, 5.28; Found: C, 67.54; H, 8.53; N, 5.43 %.

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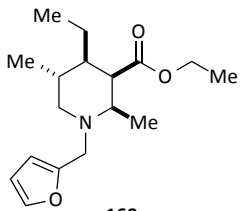
**(±)-(2*S**,3*S**,4*R**,5*R**)-Ethyl-4-ethyl-1-(furan-2-ylmethyl)-2,5-dimethyl-piperidine-3-carboxylate (169):**



**169**

Prepared from compound **143** (86 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 62 mg (71 %) as a viscous pale brown oil.

Data of **169**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.79 (d, *J* = 6.5 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H), 0.92-1.13 (m, 2H), 1.22-1.30 (m, 6H), 1.58-1.69 (m, 1H), 1.91 (t, *J* = 11.2 Hz,

1H), 2.21-2.33 (m, 1H), 2.34-2.45 (m, 1H), 2.66 (t, *J* = 4.0 Hz, 1H), 2.84 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.71 (d, *J* = 15.6 Hz, 1H), 3.97 (d, *J* = 15.6 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 6.14 (d, *J* = 3.1 Hz, 1H), 6.31 (dd, *J* = 3.1, 1.9 Hz, 1H), 7.35 (dd, *J* = 1.8, 0.8 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 11.8, 14.5, 17.3, 18.3, 22.7, 31.2, 47.2, 49.3, 49.4, 56.5, 59.6, 61.2, 109.1, 109.9, 141.8, 151.7, 172.4.

**IR** (NaCl): 3360, 2940, 1720, 1570, 1460, 1380, 1140, 1010 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{17}H_{27}NO_3$ (M = 293.20): C, 69.59; H, 9.28; N, 4.77; Found: C, 69.20; H, 8.96; N, 4.92 %.

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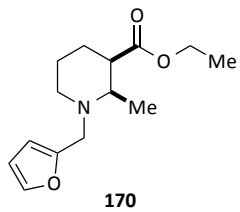
**(±)-(2*S**,3*S**)-Ethyl-1-(furan-2-ylmethyl)-2-methylpiperidine-3-carboxylate (170):**




**170**

Prepared from compound **142** (74 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 68 mg (90 %) as a viscous pale brown oil.

Data of **170**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.91 (d, *J* = 6.6 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.50-1.77 (m, 3H), 2.28-2.33 (m, 1H), 2.33-2.55 (m, 2H), 2.75-2.83 (m, 1H), 3.33-3.43 (m, 1H), 3.56 (d, *J* = 14.0 Hz, 1H), 3.67 (d, *J* = 14.0 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2 H), 6.15-6.31 (m, 2H), 7.25-7.38 (m, 1H).

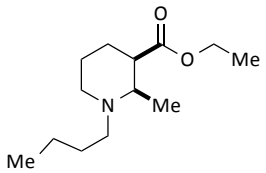
**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.0, 15.1, 21.9, 24.1, 41.1, 52.8, 54.1, 54.9, 61.1, 109.9, 110.2, 141.8, 148.1, 172.0.

**IR** (NaCl): 2940, 2800, 1720, 1460, 1370, 1280, 1150, 1020 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{14}H_{21}NO_3$ (M = ): C, 66.91; H, 8.42; N, 5.57; Found: C, 66.42; H, 8.49; N, 5.32 %.

---

**(±)-(2*S**,3*S**)-Ethyl-1-butyl-2-methylpiperidine-3-carboxylate (171):**




**171**

Prepared from compound **139** (66 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 54 mg (80 %) as a a sticky pale brown paste.

Data of **171**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.81-0.93 (m, 6H), 1.21-1.47 (m, 9H), 1.54-1.66 (m, 2H), 1.69-1.74 (m, 1H), 2.31-2.43 (m, 3H), 2.69-2.77 (m, 1H), 3.36-3.45 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H).

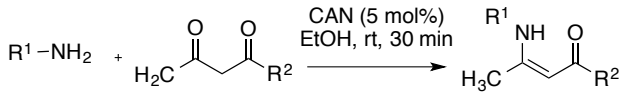
**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 5.5, 14.3, 14.5, 20.7, 21.0, 24.5, 30.1, 45.4, 46.1, 53.4, 54.7, 60.3, 174.3.

**IR** (NaCl): 3380, 1720, 1560, 1150, 1040 $cm^{-1}$.

**Elemental analysis:** Anal. Calcd for $C_{13}H_{25}NO_2$ (M = 227.19): C, 68.08; H, 11.08; N, 6.16; Found: C, 68.09; H, 10.98; N, 5.97 %.

### 7.5.4: Enantioselective synthesis of piperidines

#### 7.5.4.1: Synthesis of starting enaminones[144]

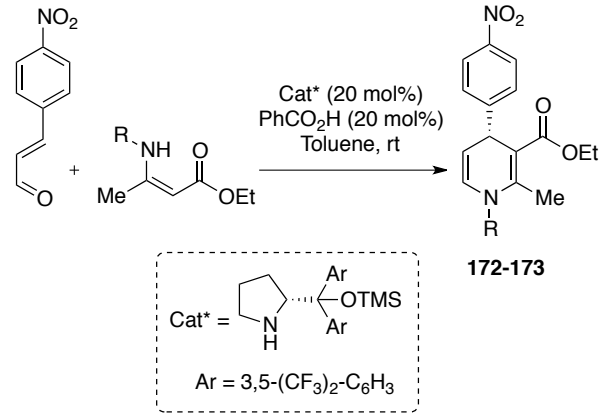



**I** = $R^1$ = Bn, $R^2$ = OEt, 98 %
**II** = $R^1$ = *n*-Pr, $R^2$ = O-$^t$Bu, 96 %

To a stirred solution of the suitable β-ketoester (1 mmol) and 27 mg (5 mol %) of CAN in ethanol (3 mL) was added the requisite primary amine (1 mmol) for 30 min at room temperature. After completion of the reaction, as monitored by TLC, the mixture was diluted with water (3 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over anhydrous $Na_2SO_4$, the solvent was removed on the rotavapor and the crude β-enaminone (almost pure by $^1$H NMR spectroscopy) was used directly for the next reaction.

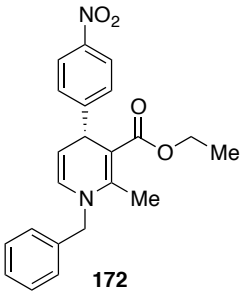
144 Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Synlett,* **2007**, 881.

### 7.5.4.2. General procedure for the organocatalytic, enantioselective synthesis of 1,4-dihydropyridines




To a solution of the Hayashi-Jørgensen catalyst (0.1 mmol, 60 mg, 20 mol%) in toluene (1.5 mL) under an Ar atmosphere was added the requisite enal (1 mmol, 2 equiv) and benzoic acid (0.1 mmol, 12 mg, 20 mol %). After 10 min of stirring, the requisite enaminone (0.5 mmol, 1 equiv) was added as a solution in toluene (0.5 mL) and the reaction mixture was stirred at room temperature for 3 h. After completion the reaction, as monitored by TLC, the reaction mixture was quenched with $NaHCO_3$ (2 mL) and extracted twice with dichloromethane (10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel, using a mixture of petroleum ether and ethyl acetate as eluent. The enantiomeric purity was calculated by HPLC analysis using chiralcel OD-H column, eluting with 10% *i*-PrOH in hexane.

**(*R*)-Ethyl 1-benzyl-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (172):**




**172**

Prepared from (*E*)-3-(4-nitrophenyl)acrylaldehyde (194 mg, 0.55 mmol, 1.1 equiv) and the suitable β-enamino ester (109 mg, 0.5 mmol, 1 equiv), yield: 132 mg (70 %) as a yellow viscous; 89 % ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% i-PrOH in hexane, 254 nm); $[\alpha]_D^{25} =$ + 328 (c 2.5 mg in 2 mL $CHCl_3$).

Data of **172**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.22 (t, *J* = 7.1 Hz, 3H), 2.59 (s, 3H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.73 (d, *J* = 16.9 Hz, 1H), 4.83 (d, *J* = 16.9 Hz, 1H), 4.92 (d, *J* = 5.4 Hz, 1H), 5.07 (dd, *J* = 7.5, 5.5 Hz, 1H), 6.6 (d, *J* = 7.6 Hz, 1H), 7.33-7.40 (m, 2H), 7.45-7.54 (m, 5H), 8.27 (d, *J* = 8.7 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.3, 16.1, 40.6, 53.9, 59.6, 99.3, 106.7, 123.8, 126.3, 127.8, 128.3, 129.1, 130.4, 137.7, 146.3, 150.0, 156.0, 168.4.

**IR** (NaCl): 2940, 1660, 1500, 1340, 1100 $cm^{-1}$

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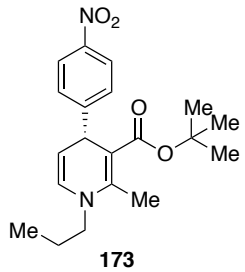
**(*R*)-*tert*-Butyl 2-methyl-4-(4-nitrophenyl)-1-propyl-1,4-dihydropyridine-3-carboxylate (173):**




**173**

Prepared from (*E*)-3-(4-nitrophenyl)acrylaldehyde (194 mg, 0.55 mmol, 1.1 equiv), the suitable β-enamino ester (177 mg, 0.5 mmol, 1 equiv), yield: 110 mg (62 %) as a yellow viscous oil; 83 % ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% i-PrOH in hexane, 254 nm); $[\alpha]_D^{25} =$ +49 (c 3.0 mg in 2 mL $CHCl_3$).

Data of **173**:

**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.93 (t, *J* = 7.1 Hz, 3H), 1.25 (s, 9H), 1.56-1.65 (m, 2H), 2.43 (s, 3H), 3.14-3.26 (m, 1H), 3.35-3.48 (m, 1H), 4.66 (d, *J* = 5.3 Hz, 1H), 4.81 (dd, *J* = 7.6, 5.3 Hz, 1H), 5.88 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 2H)

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 11.1, 15.7, 23.6, 28.3, 41.2, 52.1, 79.3, 99.9, 106.0, 123.7, 128.0, 129.7, 146.2, 148.8, 156.7, 168.0.

**IR** (NaCl): 2960, 1670, 1590, 1510, 1340, 1150 $cm^{-1}$

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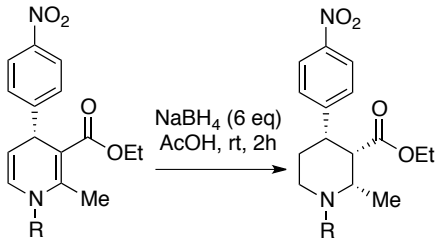
### 7.5.4.3: General procedure for the STAB reduction of enantiopure 1,4-dihydropyridines




**174-175**

The procedure for the reduction of chiral 1,4-dihydropyridine through STAB is same as described in 7.4.3: The crude product was purified by column chromatography on neutral alumina, using a mixture of petroleum ether and ethyl acetate as eluent. The enantiomeric purity was calculated by HPLC analysis using a Chiralcel OD-H column eluting with 20% *i*-PrOH in hexane.

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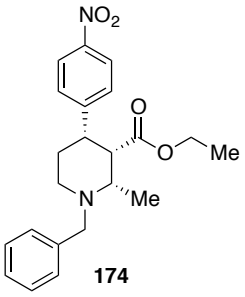
**(2*S**,3*S**,4*R**)-Ethyl 1-benzyl-2-methyl-4-(4-nitrophenyl)piperidine-3-carboxylate (174):**




**174**

Prepared from compound **171** (80 mg, 0.2 mmol, 1 equiv), $NaBH_4$ (46 mg, 1.2 mmol, 6 equiv) in 1 mL of acetic acid, yield: 68 mg (85 %) as a yellow viscous; 84% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 20% *i*-PrOH in hexane, 254 nm); $[\alpha]_D^{25} = +59$ (c 2.8 mg in 2 mL $CHCl_3$).

Data of **174**:

**$^1$H-NMR** ($CDCl_3$, 250 MHz) δ: 1.15 (t, *J* = 7.1 Hz, 3H), 1.43 (d, *J* = 6.5 Hz, 3H), 1.76 (dd, *J* = 12.0, 1.8 Hz, 1H), 2.26 (td, *J* = 11.7, 2.6 Hz, 1H), 2.84-2.89 (m, 1H), 2.94 (dd, *J* = 12.2, 4.0 Hz, 1H), 3.03 (m, 1H), 3.13 (dt, *J* = 12.8, 4.3 Hz, 1H), 3.24 (dt, *J* = 11.5, 3.1 Hz, 1H), 3.36 (d, *J* = 13.9 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 4.26 (d, *J* = 13.9 Hz, 1H), 7.35-7.58 (m, 7H), 8.28 (dd, *J* = 8.8 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 14.3, 19.1, 25.4, 44.5, 53.1, 53.6, 57.0, 58.8, 59.8, 123.5, 126.8, 128.3, 128.4, 128.7, 139.7, 146.6, 150.7, 170.8.

**IR** (NaCl): 2980, 2800, 1720, 1600, 1510, 1350, 1180, 1030 $cm^{-1}$.

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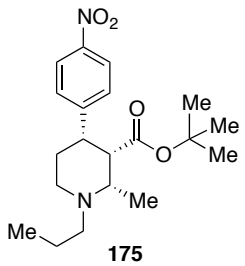
**(2*S**,3*S**,4*R**)-*tert*-Butyl 2-methyl-4-(4-nitrophenyl)-1-propylpiperidine-3-carboxylate (175):**




**175**

Prepared from compound **172** (70 mg, 0.3 mmol), $NaBH_4$ (66 mg, 1.8 mmol) in 1 mL of acetic acid, yield: 51 mg (74 %) as a yellow viscous; 83 % ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 20% i-PrOH in hexane, 254 nm); $[\alpha]_D^{25} = +51$ (c 3.6 mg in 2 mL $CHCl_3$).

Data of **175**:

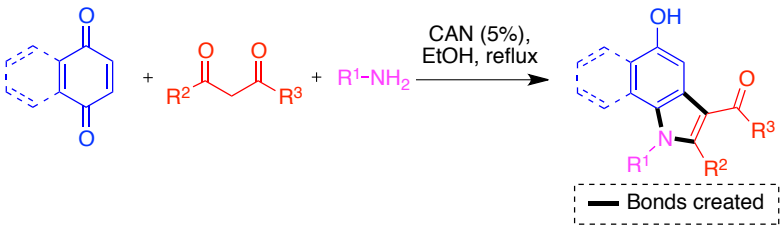
**$^{1}$H-NMR** ($CDCl_3$, 250 MHz) δ: 0.75 (t, *J* = 7.3 Hz, 3H), 1.01-1.16 (m, 12H), 1.28-1.43 (m, 2H), 1.54-1.59 (m, 1H), 2.19-2.40 (m, 2H), 2.52-2.84 (m, 5H), 3.07 (dd, *J* = 8.3, 3.0 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 63 MHz) δ: 12.1, 16.8, 18.5, 25.5, 28.0, 44.4, 52.6, 53.3, 55.2, 57.7, 80.3, 123.3, 128.6, 146.5, 150.9, 170.3.

**IR** (NaCl): 2960, 2800, 1540, 1340, 1170, 970 $cm^{-1}$.

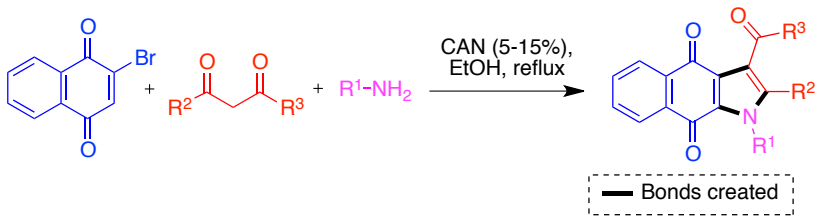
# 8. Conclusions

1. The reaction between naphthoquinone, β-dicarbonyl compounds and primary amines in refluxing ethanol containing Ce(IV) ammonium nitrate (CAN) as a Lewis acid catalyst affords 5-hydroxybenzo[*g*]indole derivatives, in a three-component version of the Nenitzescu indole synthesis. A similar reaction starting from benzoquinone affords 5-hydroxyindoles. These Lewis acid-catalyzed multicomponent Nenitzescu reactions appear to take place by a mechanism different from the standard one.

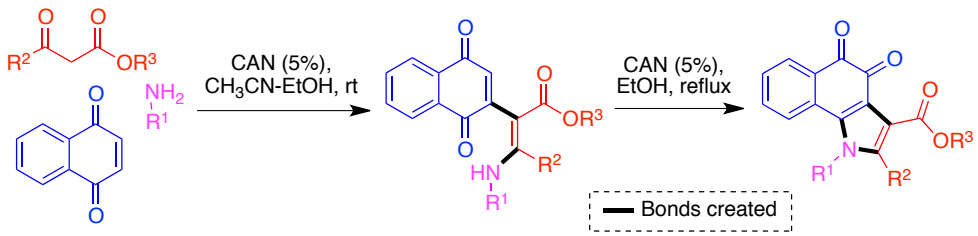



2. Suitably substituted Nenitzescu products are adequate starting materials for ring-closing metathesis reactions as complexity-generating events that allow the generation of molecular diversity by application of the build-couple-pair approach.

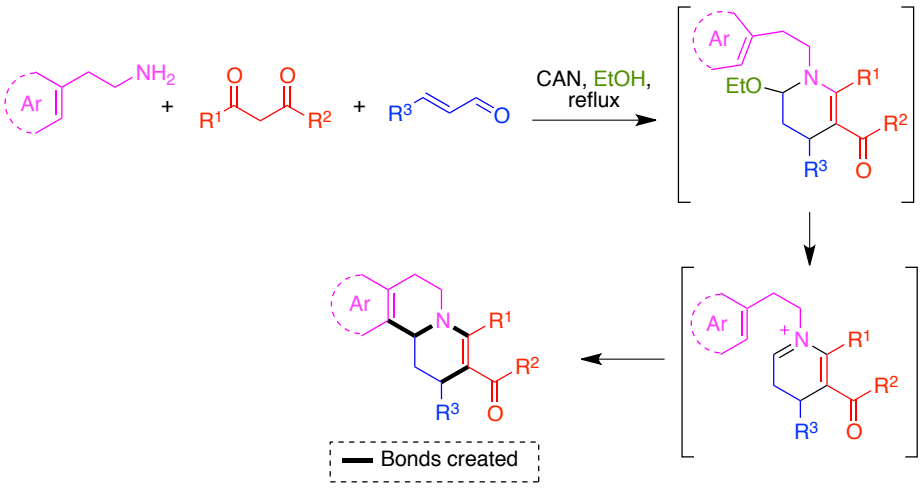

3. The replacement of the naphthoquinone component in the Nenitzescu reaction by 2-bromonaphthoquinone leads to the deviation of the course of the reaction towards a Michael-Michael domino process that affords linear benzo[*f*]indolequinones.



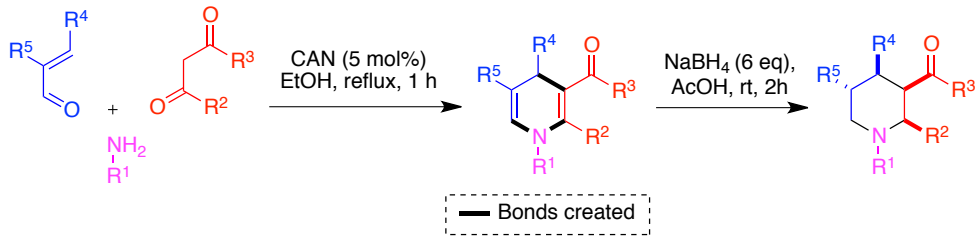

4. A slight modification in the conditions of the reaction between naphthoquinone, β-dicarbonyl compounds and primary amines consisting of the use of room temperature conditions in ethanol-acetonitrile allows the preparation of β-enaminones bearing a quinone substituent at their α position. These compounds are suitable starting materials for the preparation of tricyclic *ortho*-quinone derivatives derived from the benzo[*g*]indole system.



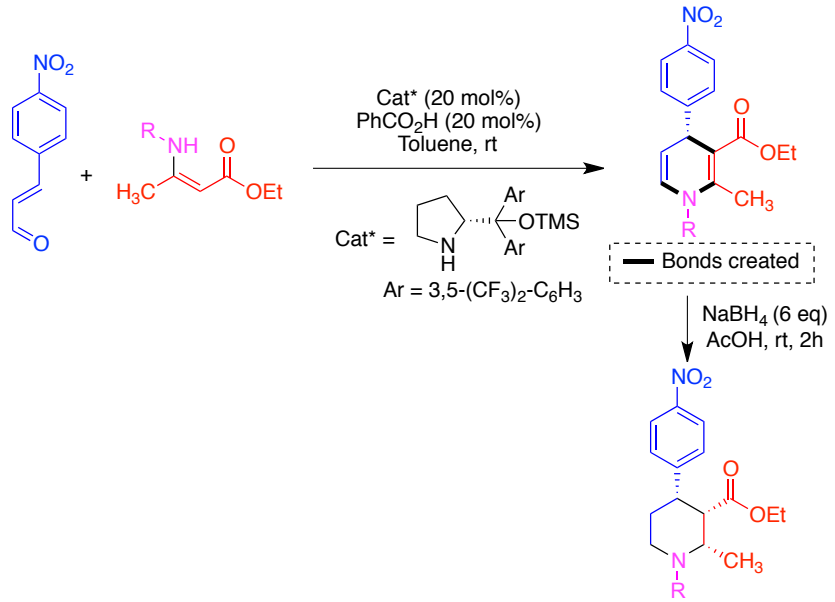
5. The combination of a multicomponent synthesis of 6-ethoxy-1,4,5,6-tetrahydropyridines previously developed by our group with the Pictet-Spengler reaction allowed the development of a one-pot synthesis of areno[*a*]quinolizines from arylethylamines, β-dicarbonyl compounds and α,β-unsaturated aldehydes in refluxing ethanol *via* the generation of two rings, two C-C bonds and two C-N bonds in a single synthetic operation.



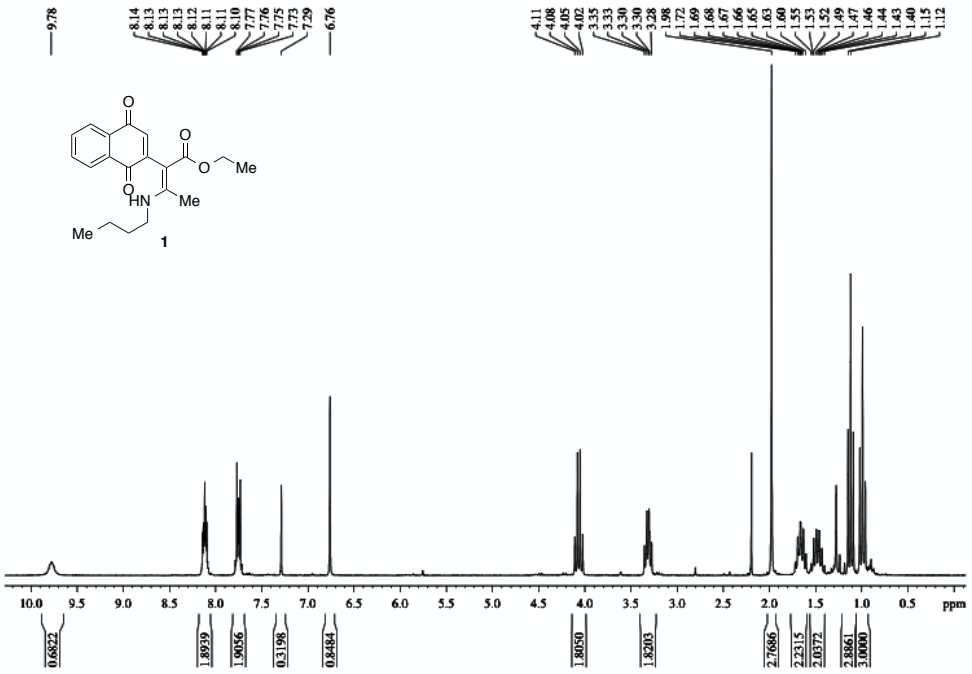

6. Dihydropyridines were readily available from primary amines, β-dicarbonyl compounds and α,β-unsaturated aldehydes *via* a modification of the above-mentioned multicomponent reaction. Their reduction with sodium triacetoxyborohydride (STAB) allowed the preparation of polysubstituted piperidine derivatives with complete diastereoselection. 6-Ethoxy-1,4,5,6-tetrahydropyridines could be reduced by the same method, affording identical results.

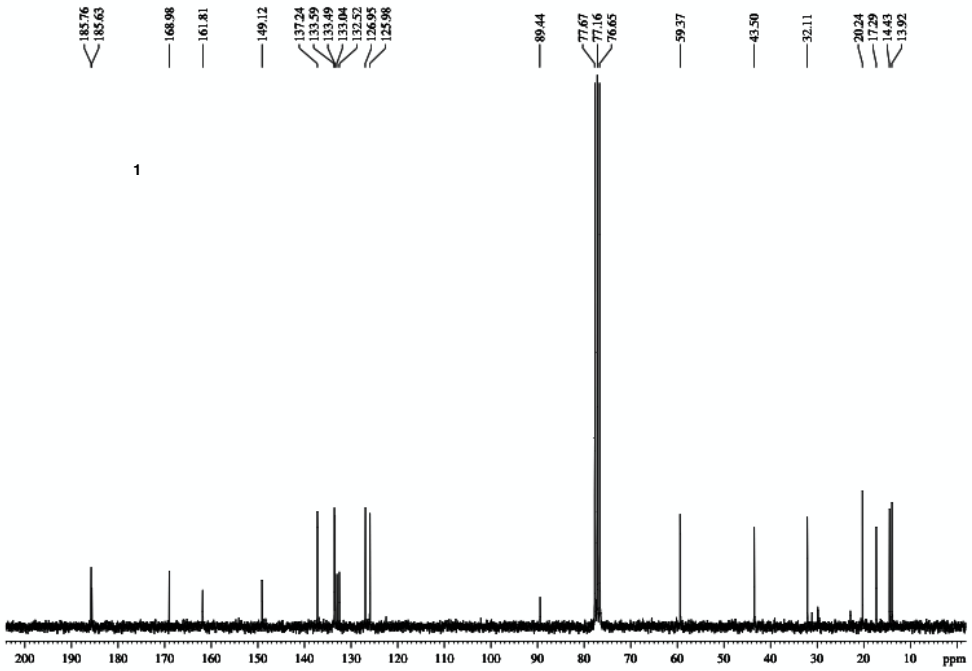


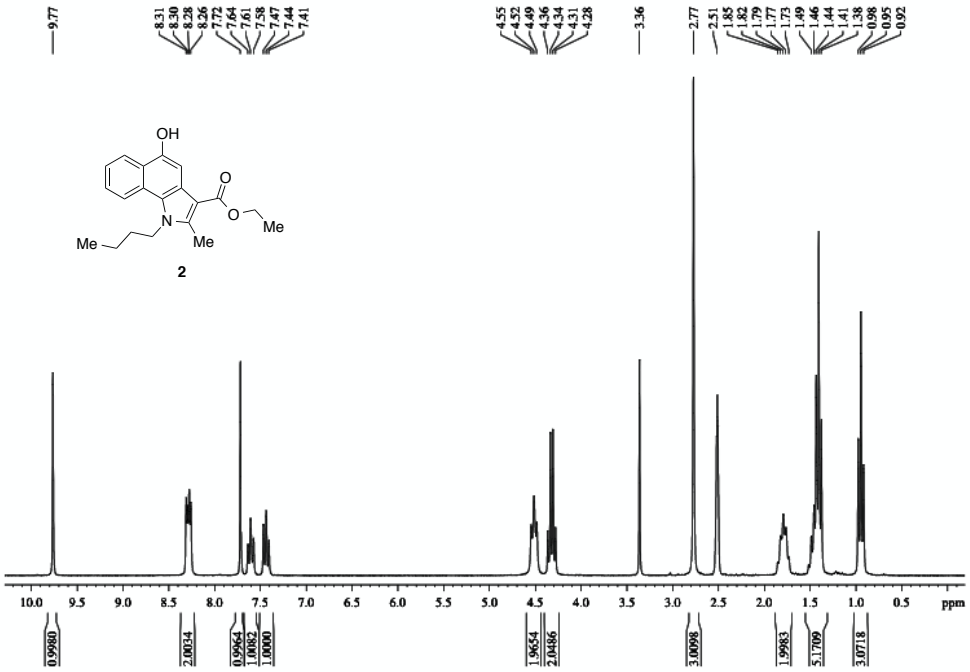

7. A preliminary study has proved the applicability of the STAB reduction method to the synthesis of chiral piperidines.

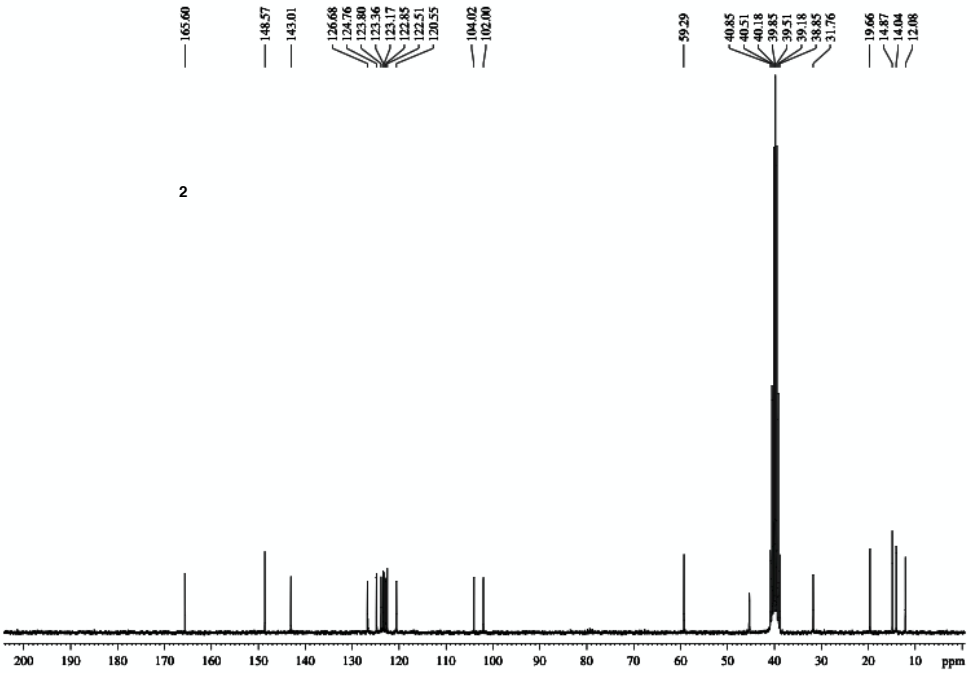


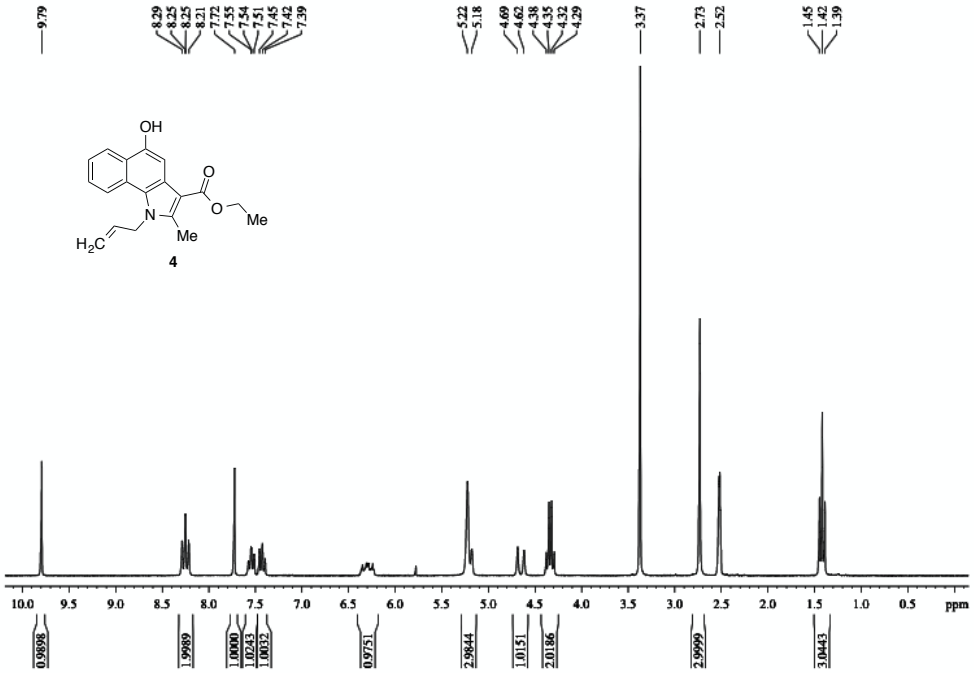
# Appendix 1: Representative spectra

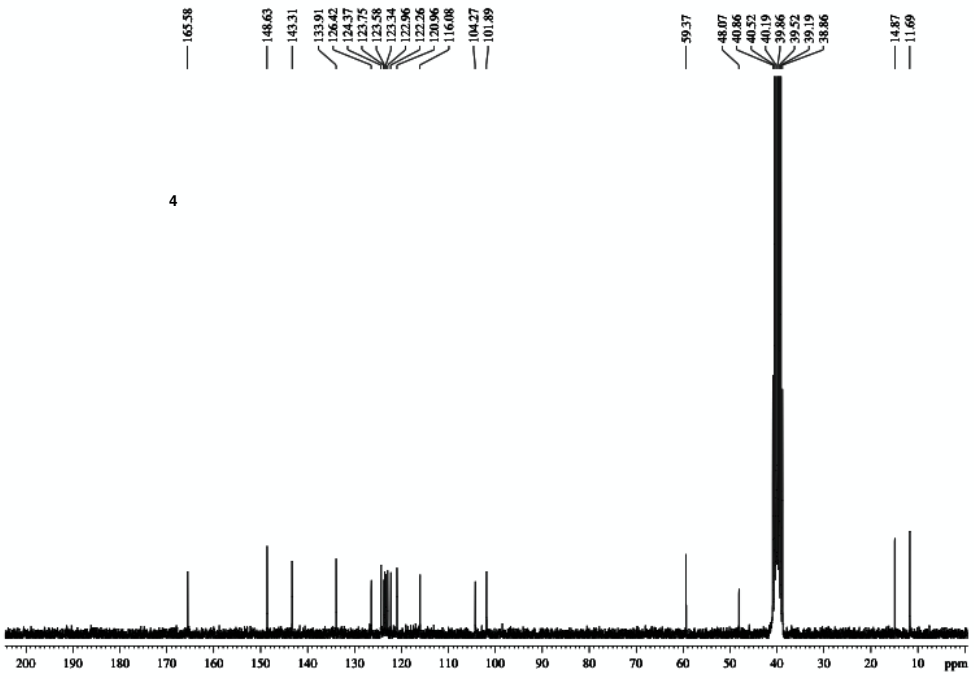

9.78
8.14
8.13
8.13
8.13
8.12
8.11
8.11
8.10
7.77
7.76
7.75
7.73
7.29
6.76
4.11
4.08
4.05
4.02
3.35
3.33
3.30
3.30
3.28
1.98
1.72
1.69
1.68
1.67
1.66
1.65
1.63
1.60
1.55
1.53
1.52
1.49
1.47
1.46
1.44
1.43
1.40
1.15
1.12
O
O
O
Me
O
HN
Me
Me
1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.6822
1.8939
1.9056
0.3198
0.8484
1.8050
1.8203
2.7686
2.2315
2.0372
2.8861
3.0000

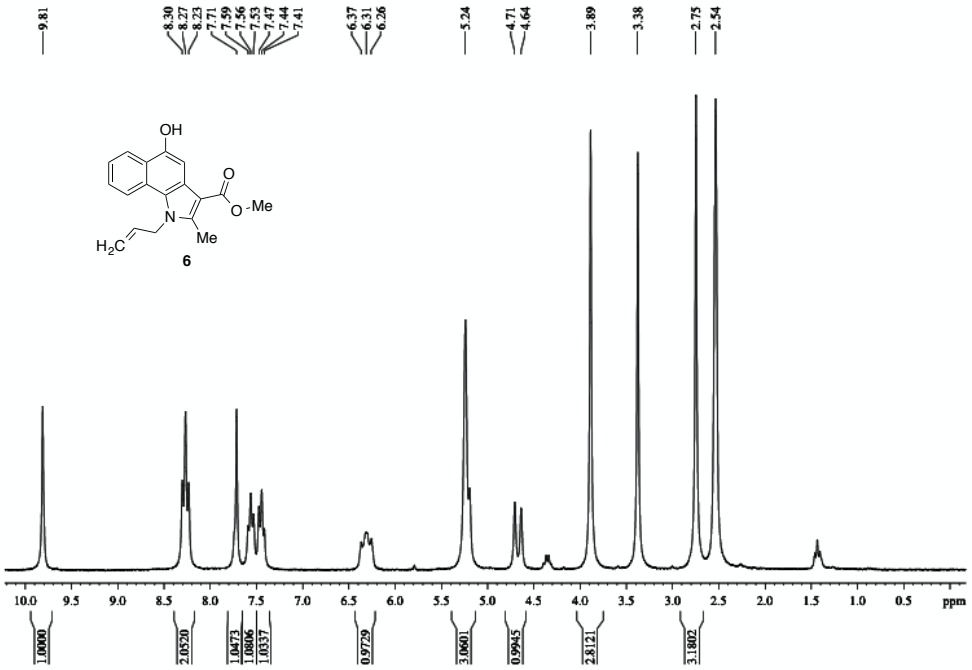

185.76
185.63
168.98
161.81
149.12
137.24
133.59
133.49
133.04
132.52
126.95
125.98
89.44
77.67
77.16
76.65
59.37
43.50
32.11
20.24
17.29
14.43
13.92
1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


9.77
8.31
8.30
8.28
8.26
7.72
7.64
7.61
7.58
7.47
7.44
7.41
4.55
4.52
4.49
4.36
4.34
4.31
4.28
3.36
2.77
2.51
1.85
1.82
1.79
1.77
1.73
1.49
1.46
1.44
1.41
1.38
0.98
0.95
0.92
OH
O
O
N
Me
Me
Me
2
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.9980
2.0034
0.9964
1.0082
1.0000
1.9654
2.0486
3.0098
1.9983
5.1709
3.0718


165.60
148.57
143.01
126.68
124.76
123.80
123.36
123.17
122.85
122.51
120.55
104.02
102.00
59.29
40.85
40.51
40.18
39.85
39.51
39.18
38.85
31.76
19.66
14.87
14.04
12.08
2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


9.79
8.29
8.25
8.25
8.21
7.72
7.55
7.54
7.51
7.45
7.42
7.39
5.22
5.18
4.69
4.62
4.38
4.35
4.32
4.29
3.37
2.73
2.52
1.45
1.42
1.39
OH
O
O
Me
N
Me
H2C
4
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.9898
1.9989
1.0000
1.0243
1.0032
0.9751
2.9844
1.0151
2.0186
2.9999
3.0443


165.58
148.63
143.31
133.91
126.42
124.37
123.75
123.58
123.34
122.96
122.26
120.96
116.08
104.27
101.89
59.37
48.07
40.86
40.52
40.19
39.86
39.52
39.19
38.86
14.87
11.69
4
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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8.30
8.27
8.23
7.71
7.59
7.56
7.53
7.47
7.44
7.41
6.37
6.31
6.26
5.24
4.71
4.64
3.89
3.38
2.75
2.54
OH
O
O
Me
N
Me
H2C
6
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.0000
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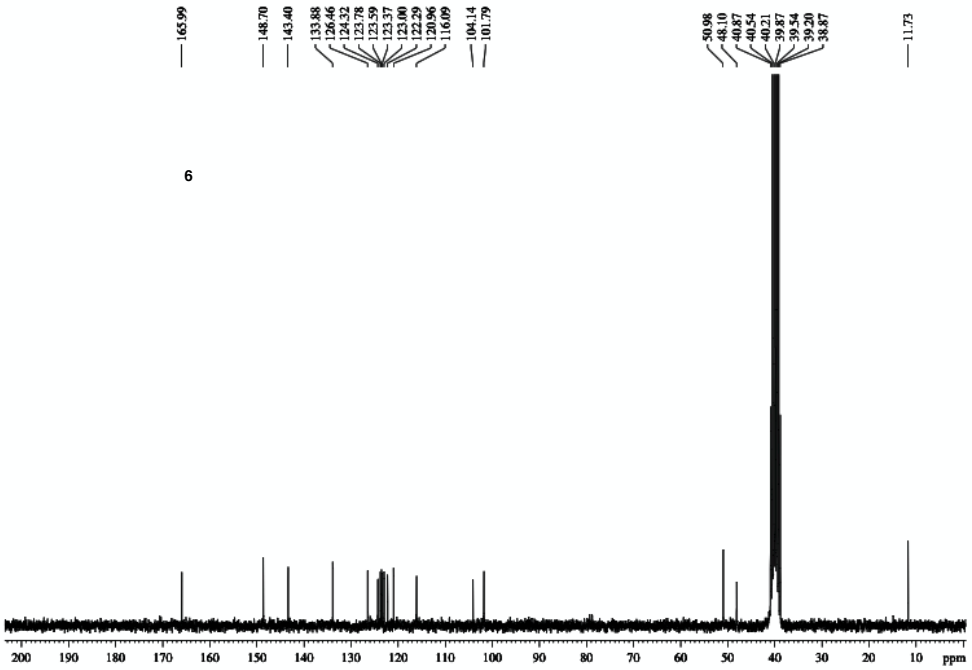
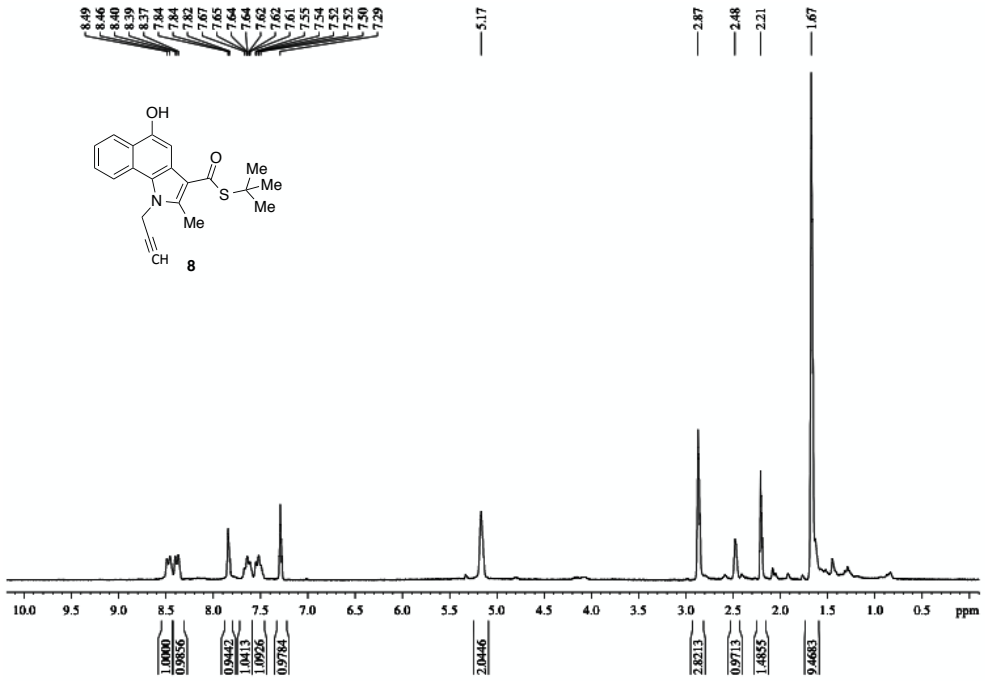
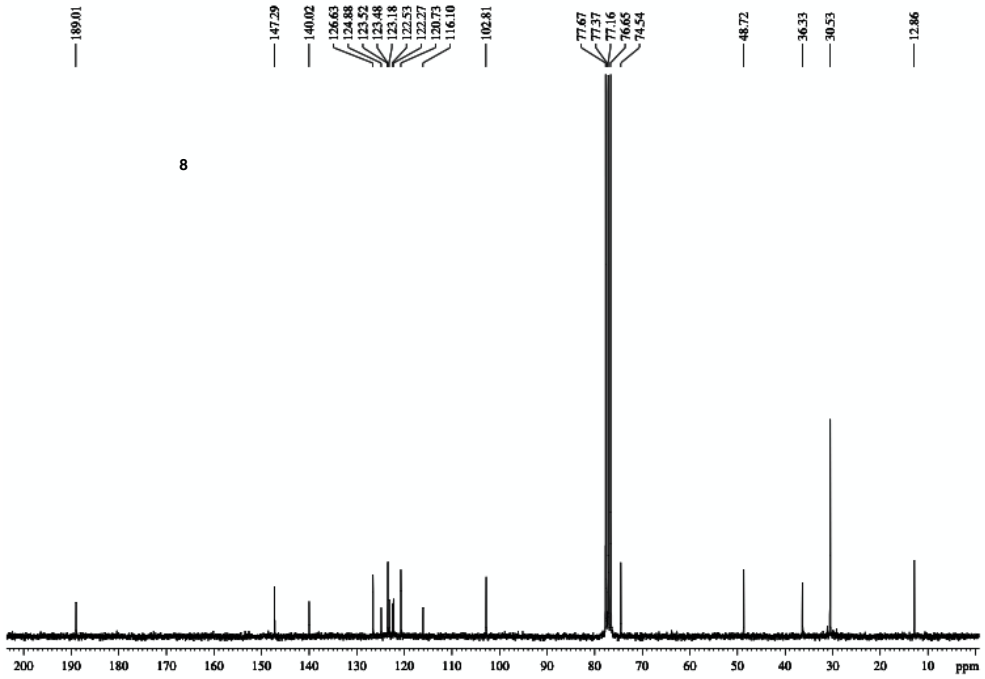
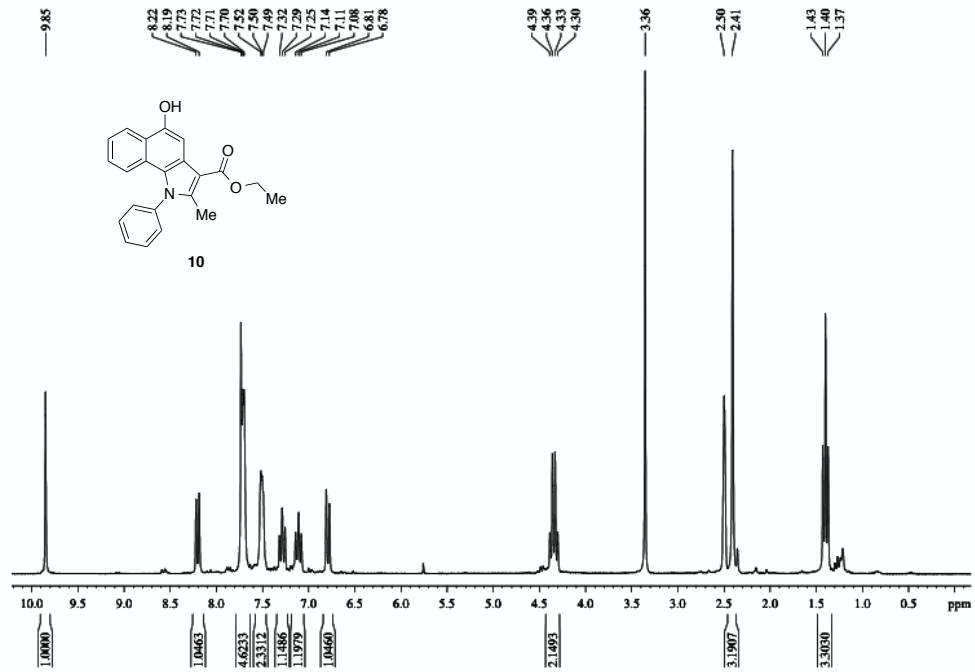
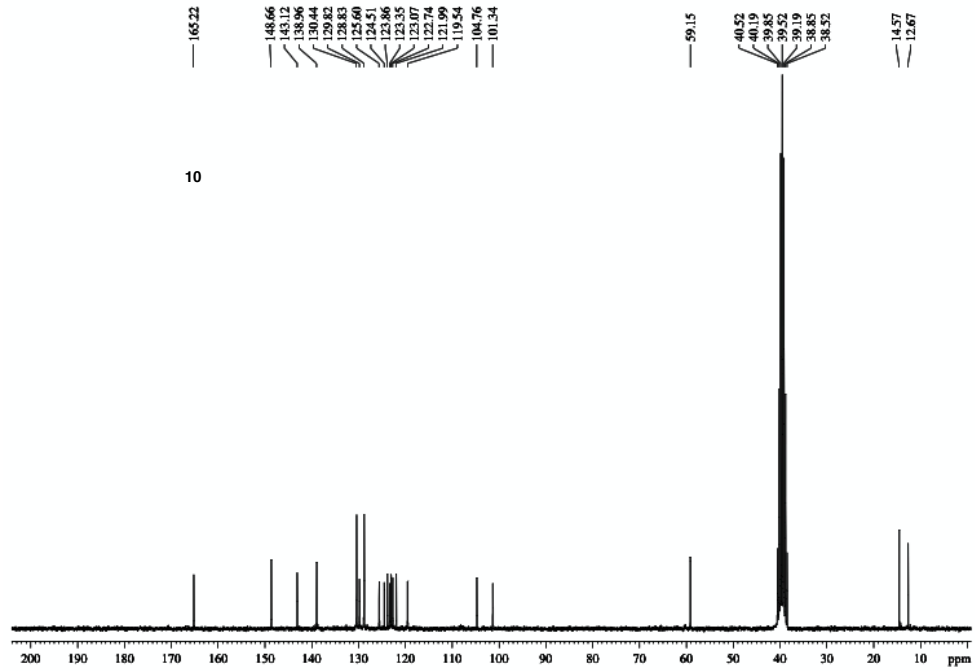
1.0473
1.0806
1.0337
0.9729
3.0601
0.9945
2.8121
3.1802

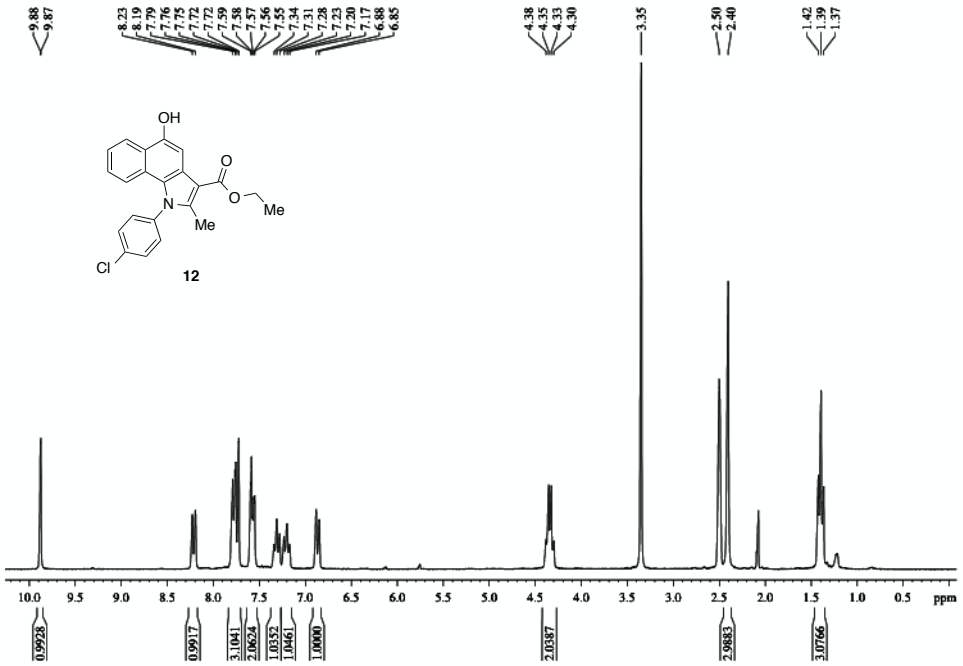

165.99
148.70
143.40
133.88
126.46
124.32
123.78
123.59
123.37
123.00
122.29
120.96
116.09
104.14
101.79
50.98
48.10
40.87
40.54
40.21
39.87
39.54
39.20
38.87
11.73
6
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

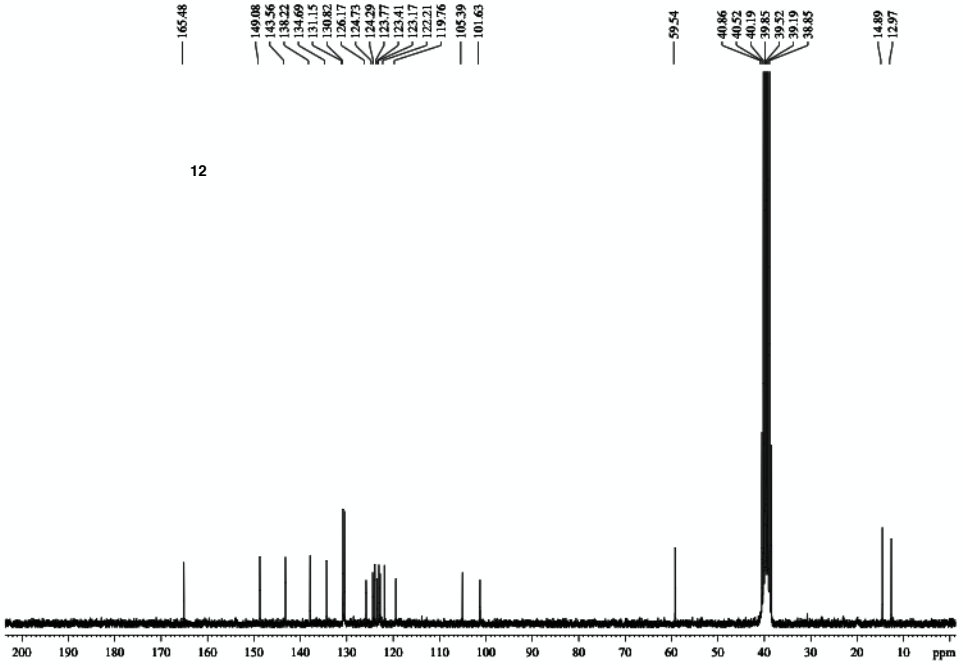

8.49
8.46
8.40
8.39
8.37
7.84
7.84
7.82
7.67
7.65
7.64
7.64
7.62
7.62
7.61
7.55
7.54
7.52
7.52
7.50
7.29
5.17
2.87
2.48
2.21
1.67
OH
O
Me
Me
Me
S
N
Me
CH
8
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000
0.9856
0.9442
1.0413
1.0926
0.9784
2.0446
2.8213
0.9713
1.4855
9.4683

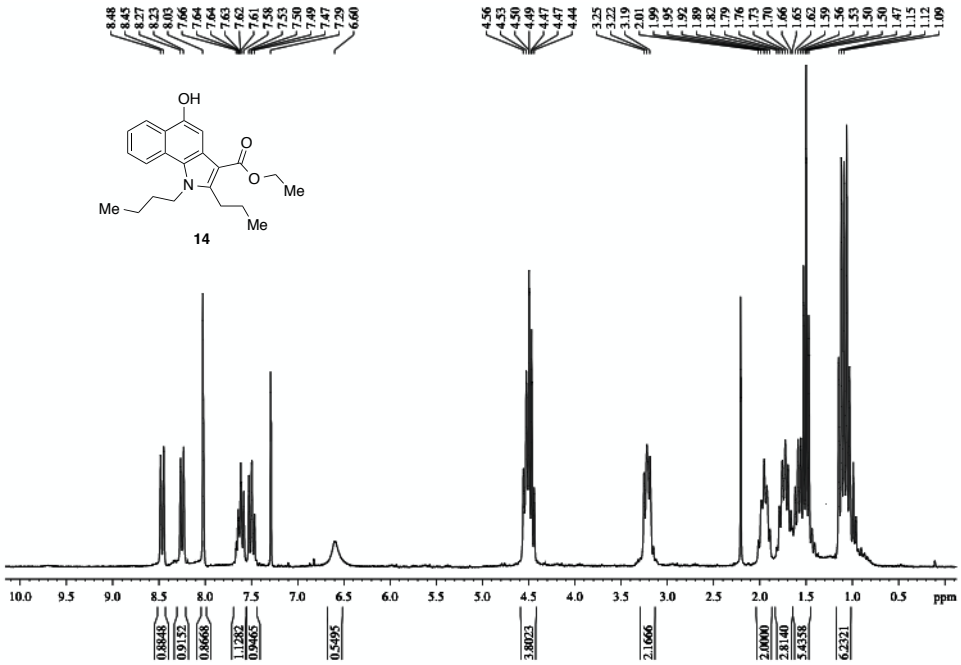

189.01
147.29
140.02
126.63
124.88
123.52
123.48
123.18
122.53
122.27
120.73
116.10
102.81
77.67
77.37
77.16
76.65
74.54
48.72
36.33
30.53
12.86
8
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

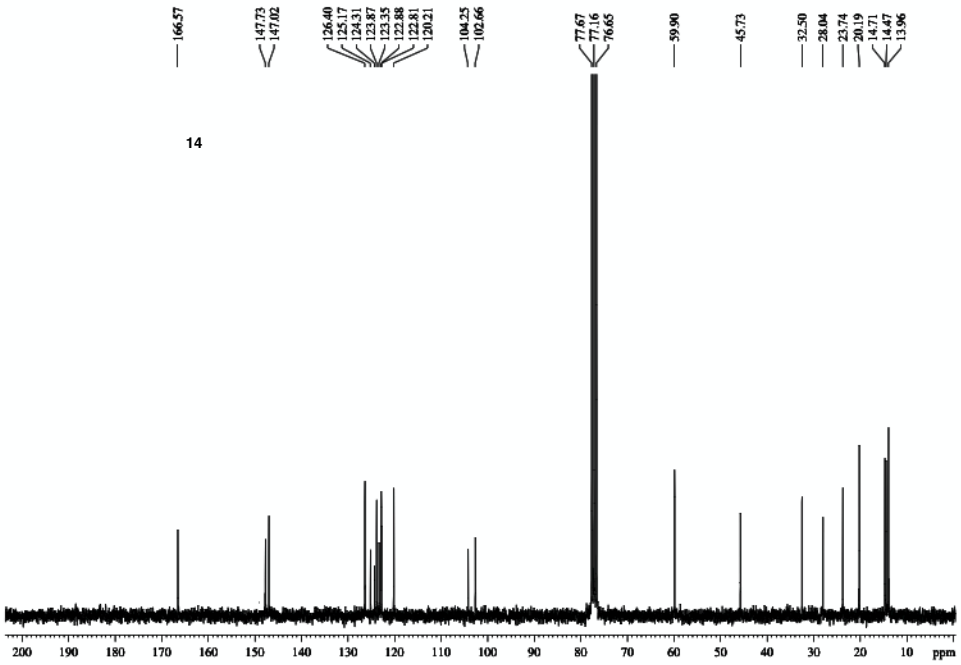

9.85
8.22
8.19
7.73
7.72
7.71
7.70
7.52
7.50
7.49
7.32
7.29
7.25
7.14
7.11
7.08
6.81
6.78
4.39
4.36
4.33
4.30
3.36
2.50
2.41
1.43
1.40
1.37
OH
O
O
Me
N
Me
10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000
1.0463
4.6233
2.3312
1.1486
1.1979
1.0460
2.1493
3.1907
3.3050

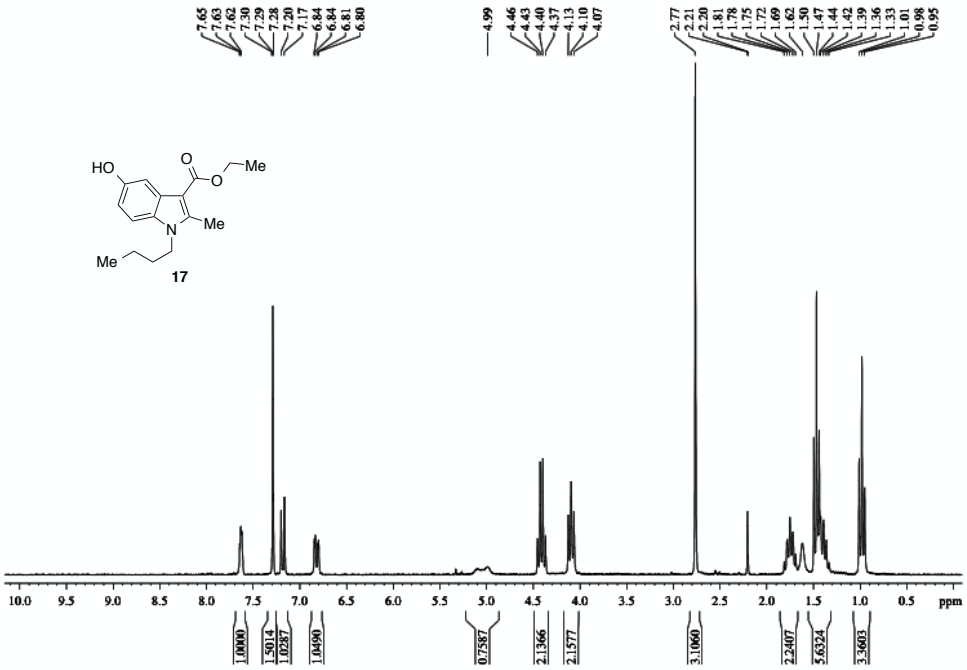

165.22
148.66
143.12
138.96
130.44
129.82
128.83
125.60
124.51
123.86
123.35
123.07
122.74
121.99
119.54
104.76
101.34
59.15
40.52
40.19
39.85
39.52
39.19
38.85
38.52
14.57
12.67
10
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

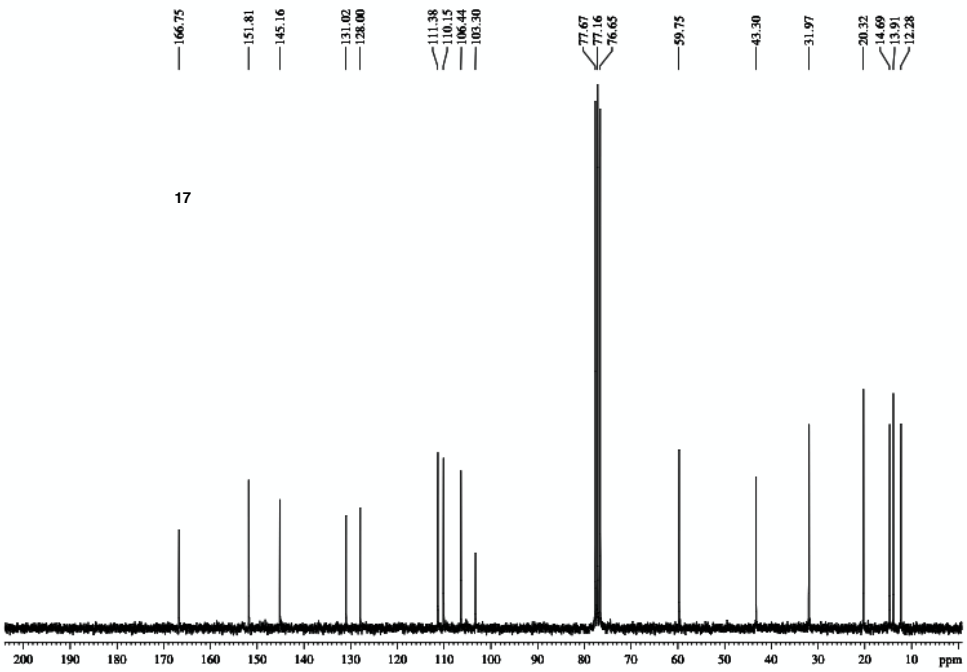

9.88
9.87
8.23
8.19
7.79
7.76
7.75
7.72
7.72
7.59
7.58
7.57
7.56
7.55
7.34
7.31
7.28
7.23
7.20
7.17
6.88
6.85
4.38
4.35
4.33
4.30
3.35
2.50
2.40
1.42
1.39
1.37
OH
O
O
N
Me
Me
Cl
12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.9928
0.9917
3.1041
2.0624
1.0352
1.0461
1.0000
2.0387
2.9883
3.0766

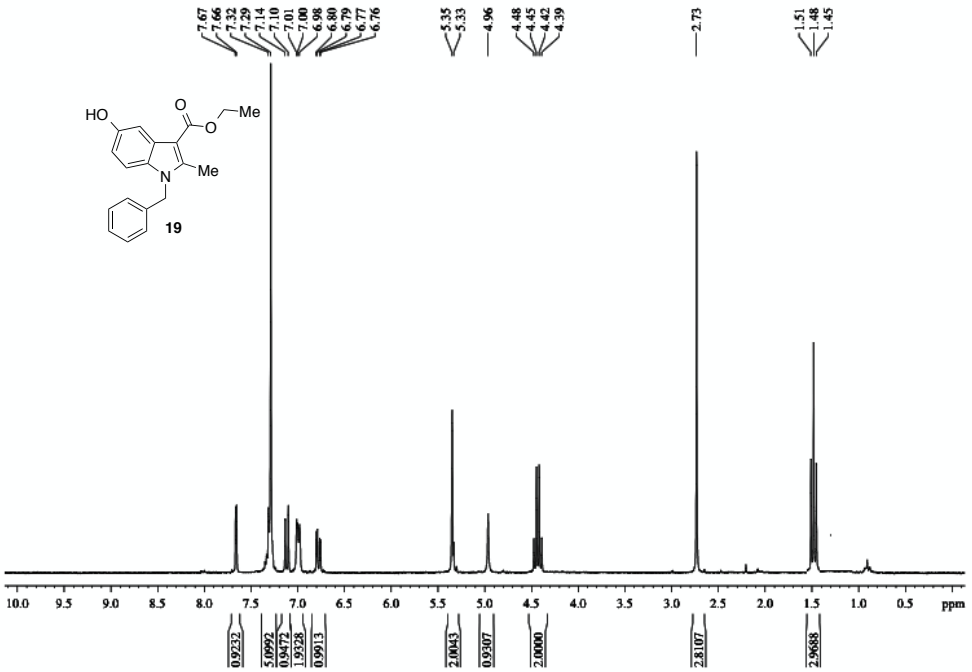

165.48
149.08
143.56
138.22
134.69
131.15
130.82
126.17
124.73
124.29
123.77
123.41
123.17
122.21
119.76
105.39
101.63
59.54
40.86
40.52
40.19
39.85
39.52
39.19
38.85
14.89
12.97
12
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.48
8.45
8.27
8.23
8.03
7.66
7.64
7.64
7.63
7.62
7.61
7.58
7.53
7.50
7.49
7.47
7.29
6.60
4.56
4.53
4.50
4.49
4.47
4.47
4.44
3.25
3.22
3.19
2.01
1.99
1.95
1.92
1.89
1.82
1.79
1.76
1.73
1.70
1.66
1.65
1.62
1.59
1.56
1.53
1.50
1.50
1.47
1.15
1.12
1.09
OH
O
O
N
Me
Me
Me
14
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8848
0.9152
0.8668
1.1282
0.9465
0.5495
3.8023
2.1666
2.0000
2.8140
5.4358
6.2321


166.57
147.73
147.02
126.40
125.17
124.31
123.87
123.35
122.88
122.81
120.21
104.25
102.66
77.67
77.16
76.65
59.90
45.73
32.50
28.04
23.74
20.19
14.71
14.47
13.96
14
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.65
7.63
7.62
7.30
7.29
7.28
7.20
7.17
6.84
6.84
6.81
6.80
4.99
4.46
4.43
4.40
4.37
4.13
4.10
4.07
2.77
2.21
2.20
1.81
1.78
1.75
1.72
1.69
1.62
1.50
1.47
1.44
1.42
1.39
1.36
1.33
1.01
0.98
0.95
HO
O
O
Me
Me
N
Me
17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000
1.5014
1.0287
1.0490
0.7587
2.1366
2.1577
3.1060
2.2407
5.6324
3.3603


166.75
151.81
145.16
131.02
128.00
111.38
110.15
106.44
103.30
77.67
77.16
76.65
59.75
43.30
31.97
20.32
14.69
13.91
12.28
17
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.66
7.32
7.29
7.14
7.10
7.01
7.00
6.98
6.80
6.79
6.77
6.76
5.35
5.33
4.96
4.48
4.45
4.42
4.39
2.73
1.51
1.48
1.45
HO
O
O
Me
Me
N
19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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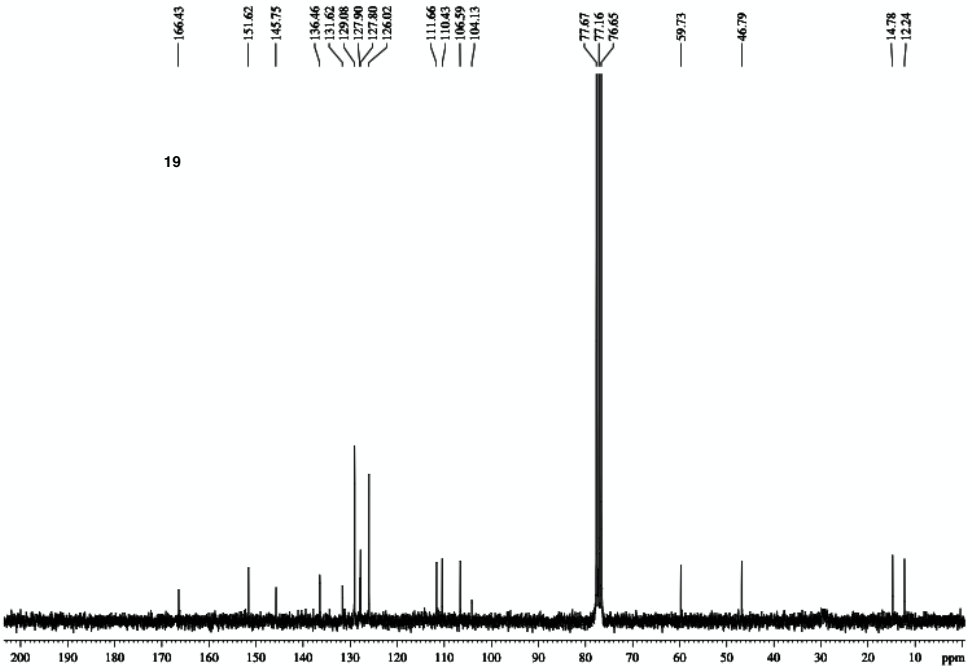
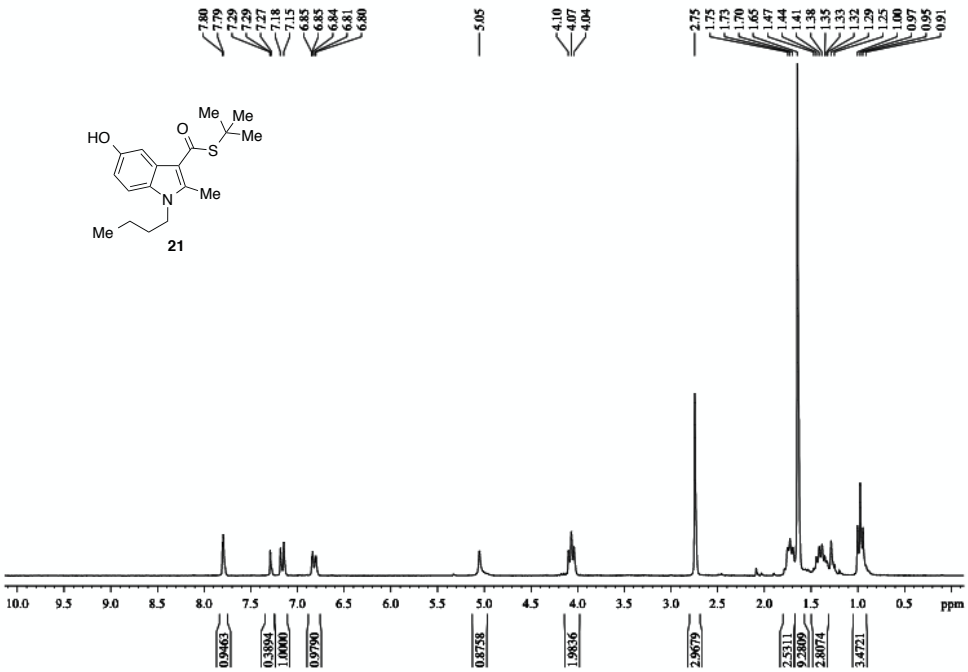
5.0992
0.9472
1.9528
0.9913
2.0043
0.9307
2.0000
2.8107
2.9688


166.43
151.62
145.75
136.46
131.62
129.08
127.90
127.80
126.02
111.66
110.43
106.59
104.13
77.67
77.16
76.65
59.73
46.79
14.78
12.24
19
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.80
7.79
7.29
7.29
7.27
7.18
7.15
6.85
6.85
6.84
6.81
6.80
5.05
4.10
4.07
4.04
2.75
1.75
1.73
1.70
1.65
1.47
1.44
1.41
1.38
1.35
1.33
1.32
1.29
1.25
1.00
0.97
0.95
0.91
HO
O
S
Me
Me
Me
Me
N
Me
21
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.9463
0.3894
1.0000
0.9790
0.8758
1.9836
2.9679
2.5311
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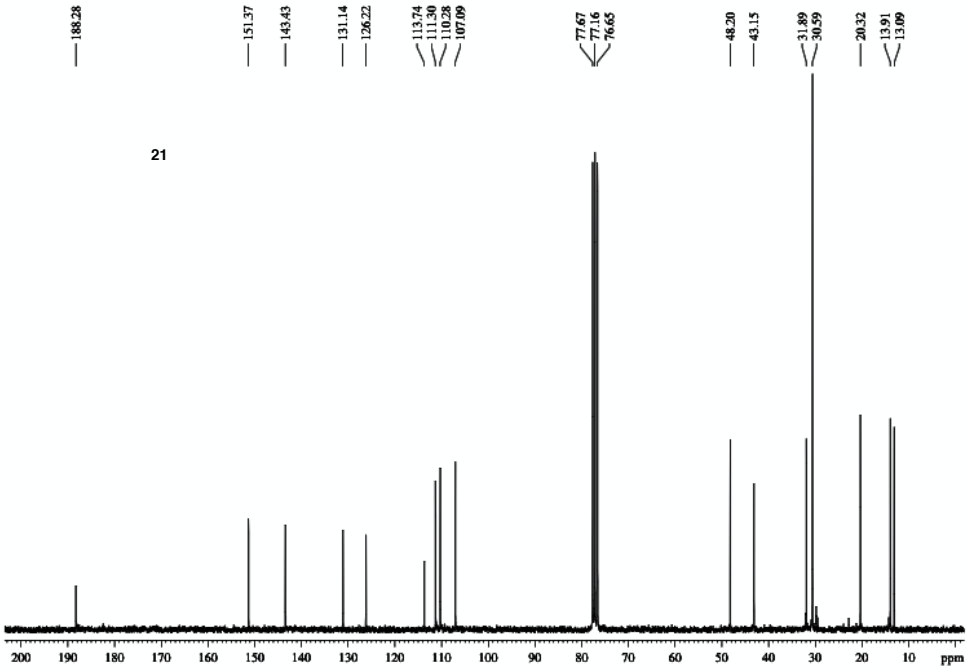
2.8074
3.4721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110.28
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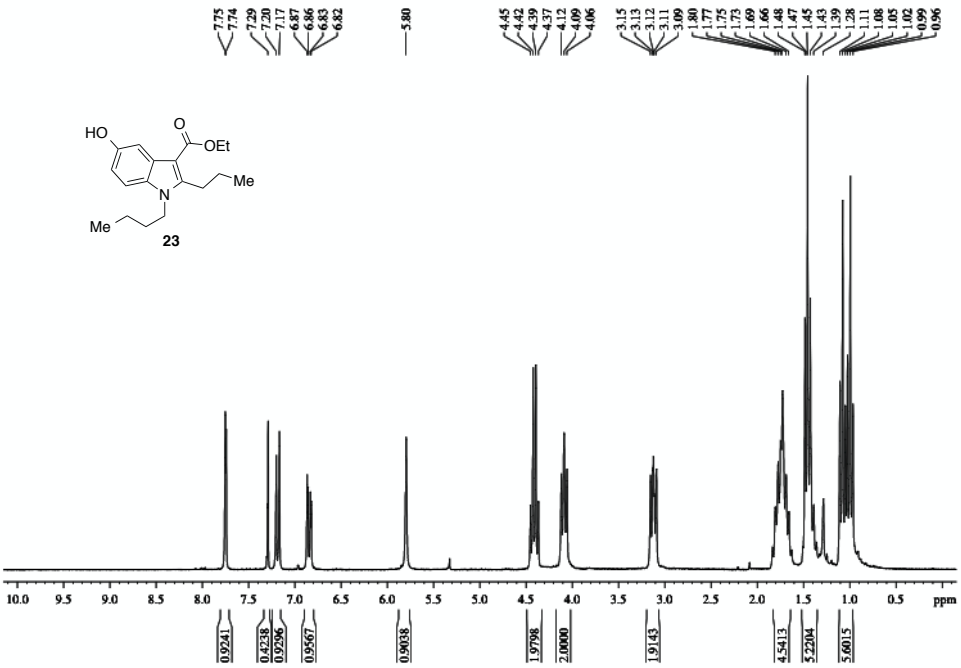
30.59
20.32
13.91
13.09
21
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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4.45
4.42
4.39
4.37
4.12
4.09
4.06
3.15
3.13
3.12
3.11
3.09
1.80
1.77
1.75
1.73
1.69
1.66
1.48
1.47
1.45
1.43
1.39
1.28
1.11
1.08
1.05
1.02
0.99
0.96
HO
O
OEt
Me
N
Me
23
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.9241
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0.9567
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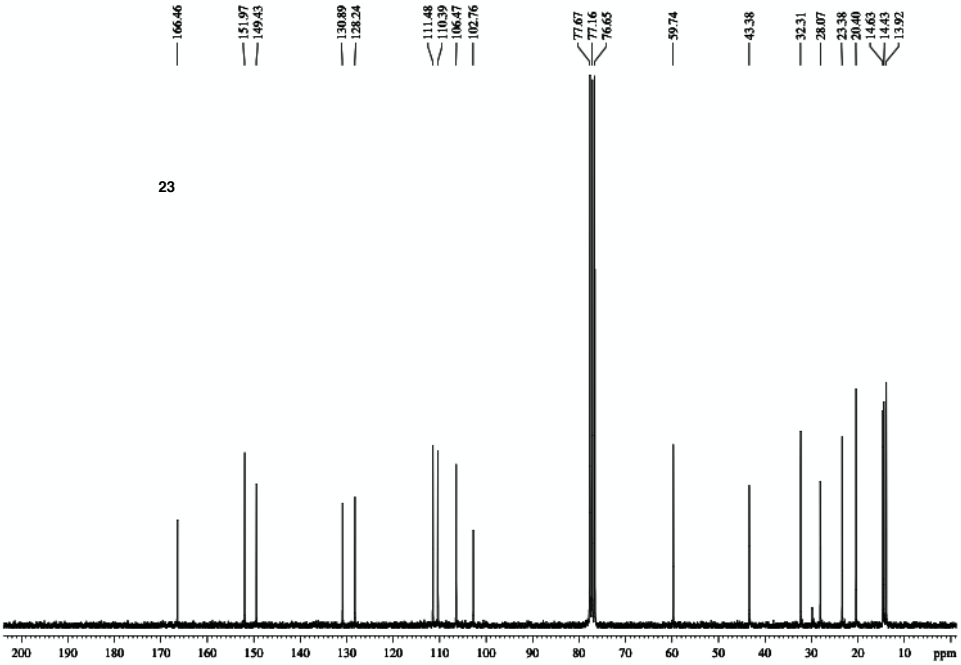
2.0000
1.9143
4.5413
5.2204
5.6015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106.47
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77.67
77.16
76.65
59.74
43.38
32.31
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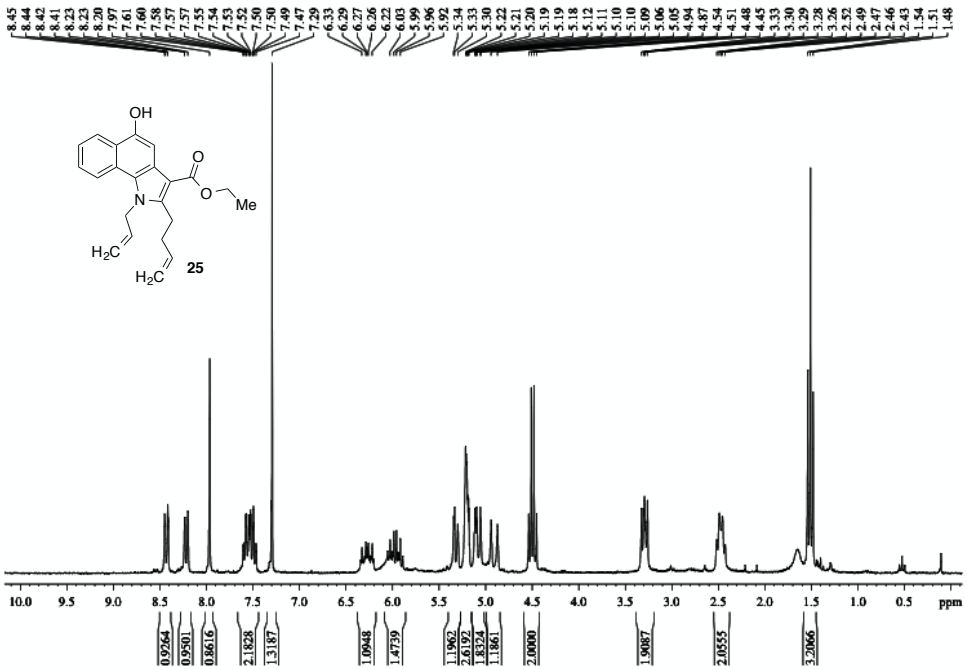
23.38
20.40
14.63
14.43
13.92
23
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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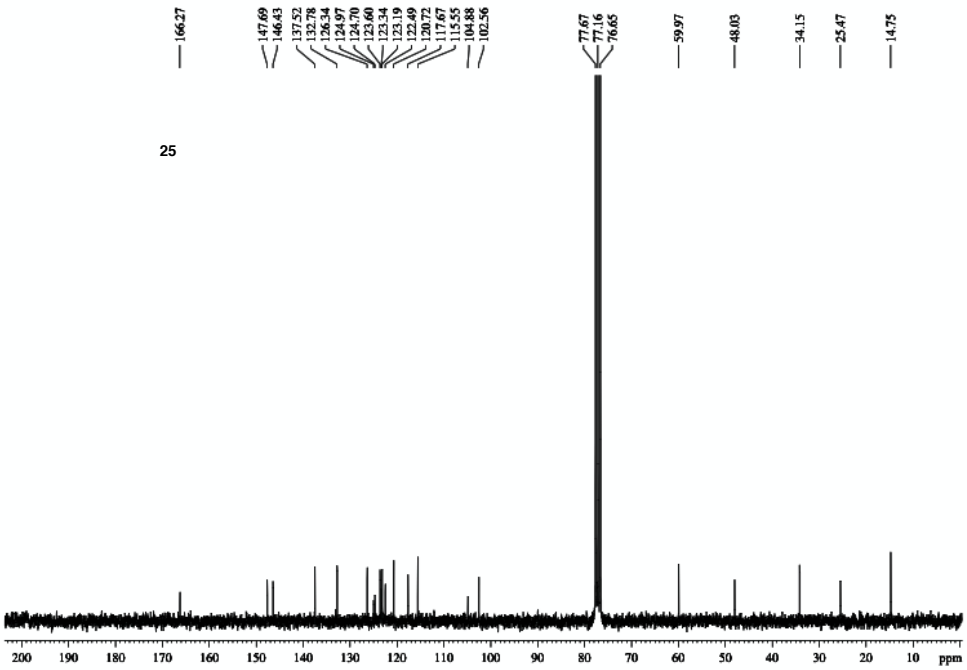
O
O
Me
N
H2C
H2C
25
ppm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122.49
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117.67
115.55
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77.67
77.16
76.65
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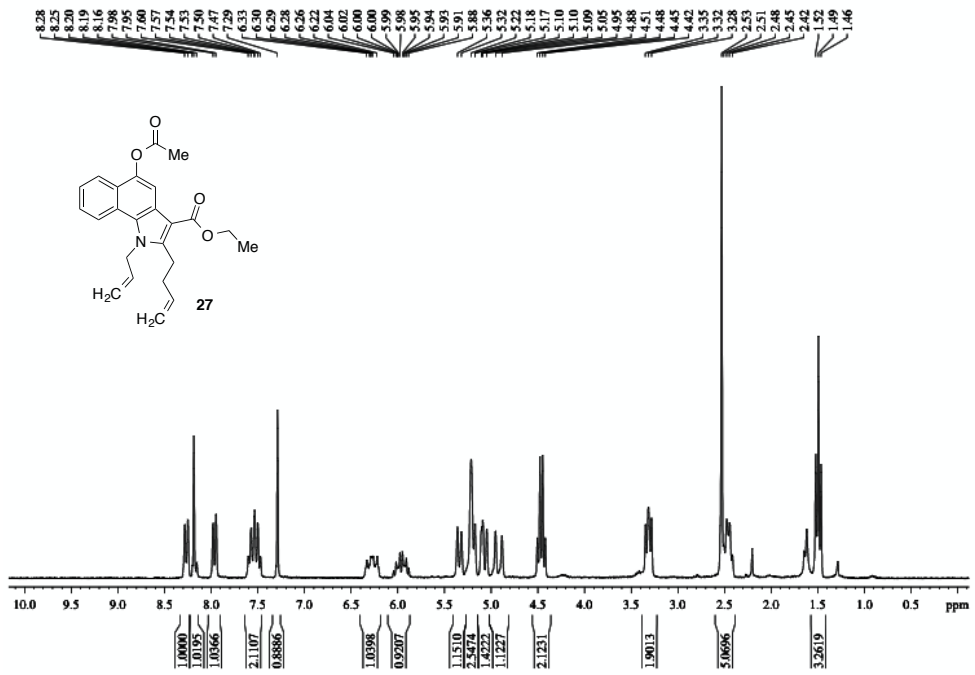
48.03
34.15
25.47
14.75
25
ppm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8.25
8.20
8.19
8.16
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7.57
7.54
7.53
7.50
7.47
7.29
6.33
6.30
6.29
6.28
6.26
6.22
6.04
6.02
6.00
6.00
5.99
5.98
5.95
5.94
5.93
5.91
5.88
5.36
5.32
5.22
5.18
5.17
5.10
5.10
5.09
5.05
4.95
4.88
4.51
4.48
4.45
4.42
3.35
3.32
3.28
2.53
2.51
2.48
2.45
2.42
1.52
1.49
1.46
O
O
Me
O
O
Me
N
H2C
H2C
27
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.0000
1.0195
1.0366
2.1107
0.8886
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1.1510
2.4474
1.4222
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2.1231
1.9013
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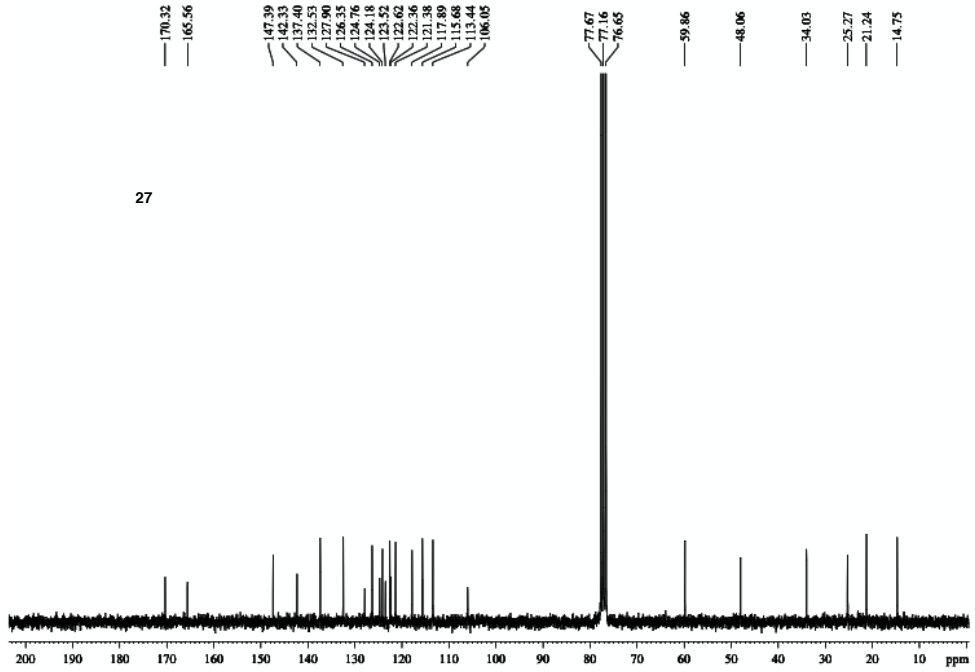
3.2619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132.53
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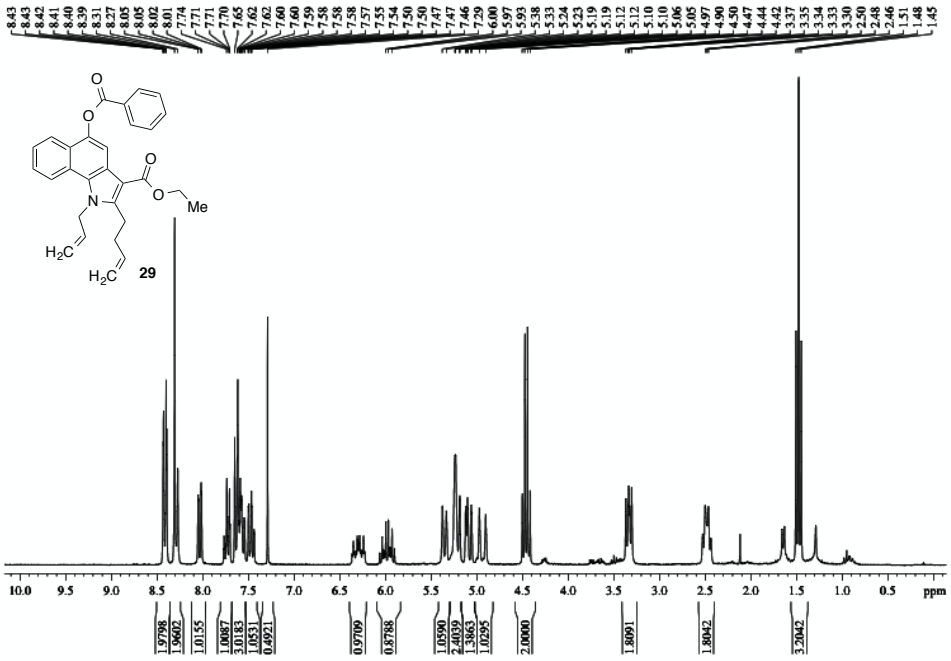
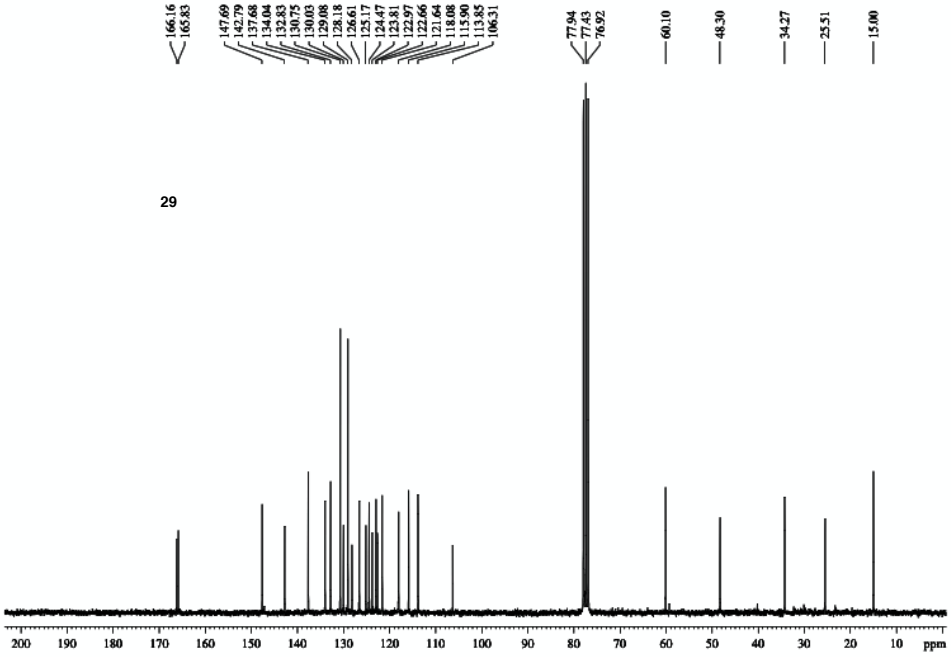
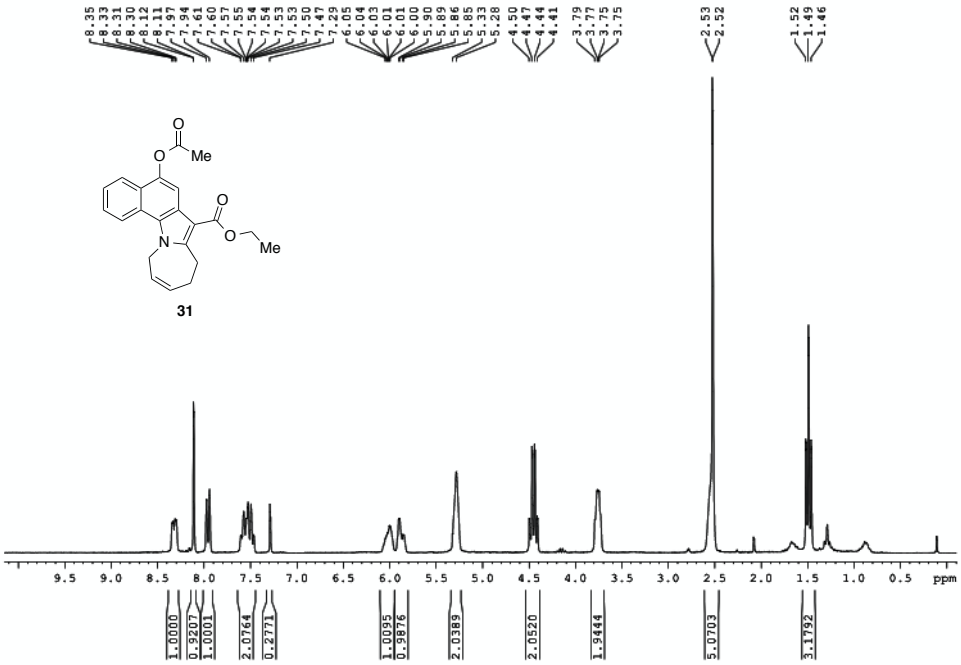
126.35
124.76
124.18
123.52
122.62
122.36
121.38
117.89
115.68
113.44
106.05
77.67
77.16
76.65
59.86
48.06
34.03
25.27
21.24
14.75
27
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


8.43 8.43 8.42 8.41 8.40 8.39 8.31 8.27 8.05 8.05 8.02 8.01 7.74 7.71 7.71 7.70 7.65 7.62 7.62 7.60 7.60 7.59 7.58 7.58 7.58 7.57 7.55 7.54 7.50 7.50 7.47 7.47 7.46 7.29 6.00 5.97 5.93 5.38 5.33 5.24 5.23 5.19 5.19 5.12 5.12 5.10 5.10 5.06 5.05 4.97 4.90 4.50 4.47 4.44 4.42 3.37 3.35 3.34 3.33 3.30 2.50 2.48 2.46 1.51 1.48 1.45
O
O
N
O
O
Me
H2C
H2C
29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.9798 1.9602 1.0155 1.0087 3.0183 1.0531 0.4921 0.9709 0.8788 1.0590 2.4039 1.3863 1.0295 2.0000 1.8091 1.8042 3.2042


166.16 165.83 147.69 142.79 137.68 134.04 132.83 130.75 130.03 129.08 128.18 126.61 125.17 124.47 123.81 122.97 122.66 121.64 118.08 115.90 113.85 106.31 77.94 77.43 76.92 60.10 48.30 34.27 25.51 15.00
29
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.33
8.31
8.30
8.12
8.11
7.97
7.94
7.61
7.60
7.57
7.55
7.54
7.54
7.53
7.53
7.50
7.47
7.29
6.05
6.04
6.03
6.01
6.01
6.00
5.90
5.89
5.86
5.85
5.33
5.28
4.50
4.47
4.44
4.41
3.79
3.77
3.75
3.75
2.53
2.52
1.52
1.49
1.46
O
O
Me
O
O
Me
N
31
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000
0.9207
1.0001
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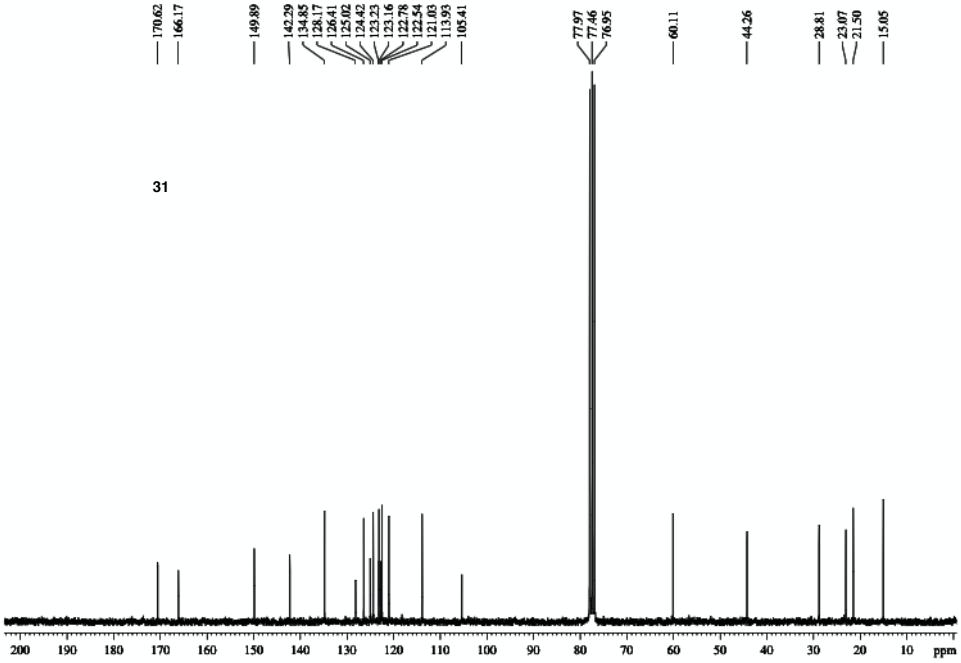
0.2771
1.0095
0.9876
2.0389
2.0520
1.9444
5.0703
3.1792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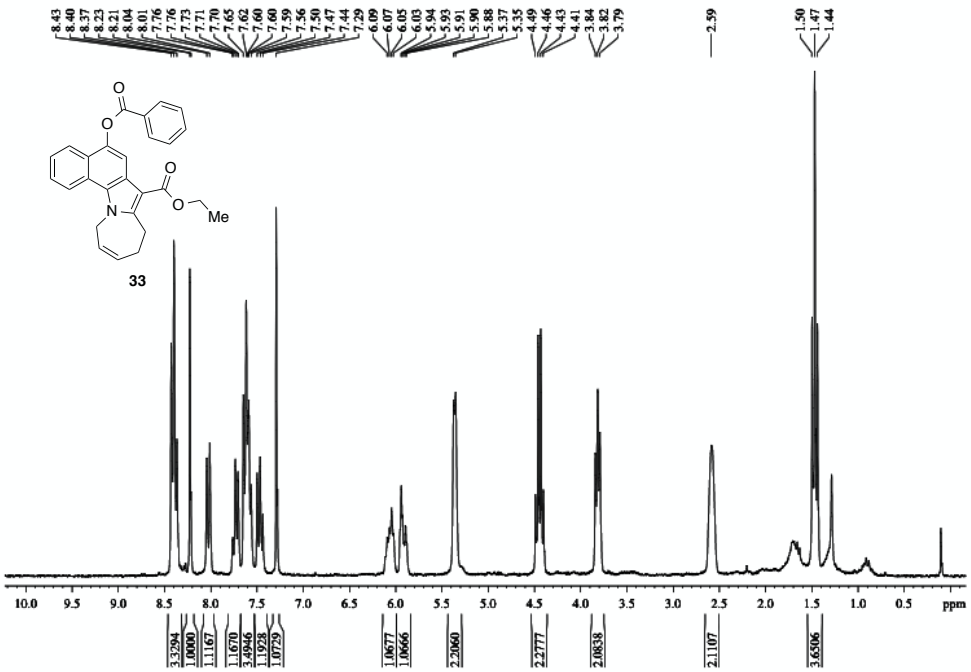
149.89
142.29
134.85
128.17
126.41
125.02
124.42
123.23
123.16
122.78
122.54
121.03
113.93
105.41
77.97
77.46
76.95
60.11
44.26
28.81
23.07
21.50
15.05
31
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.40
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8.04
8.01
7.76
7.76
7.73
7.71
7.70
7.65
7.62
7.60
7.60
7.59
7.56
7.50
7.47
7.44
7.29
6.09
6.07
6.05
6.03
5.94
5.93
5.91
5.90
5.88
5.37
5.35
4.49
4.46
4.43
4.41
3.84
3.82
3.79
2.59
1.50
1.47
1.44
O
O
O
O
N
Me
33
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.3294
1.0000
1.1167
1.1670
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1.0666
2.2060
2.2777
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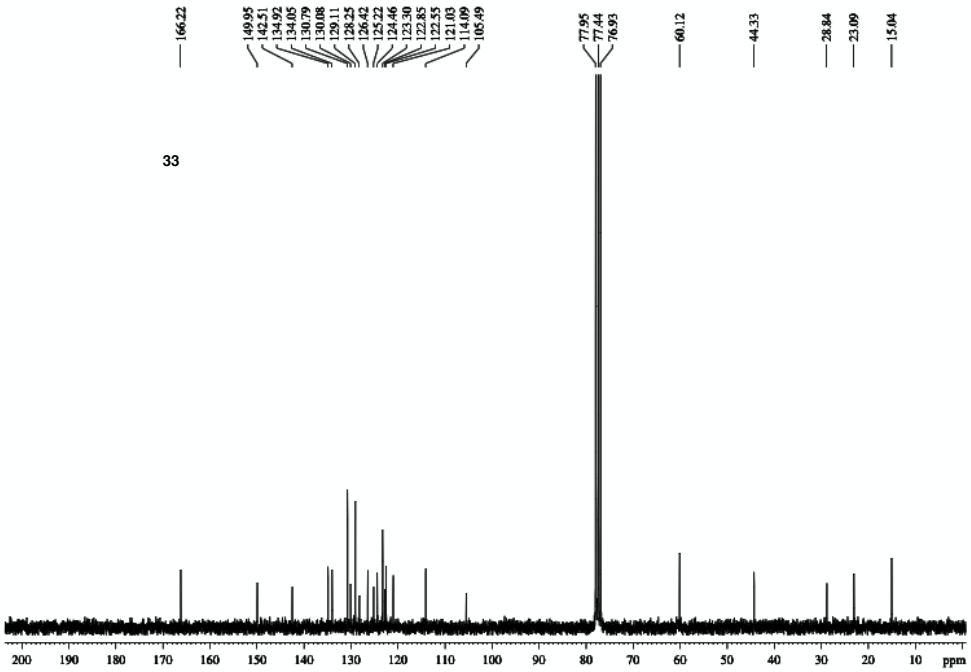
2.1107
3.6506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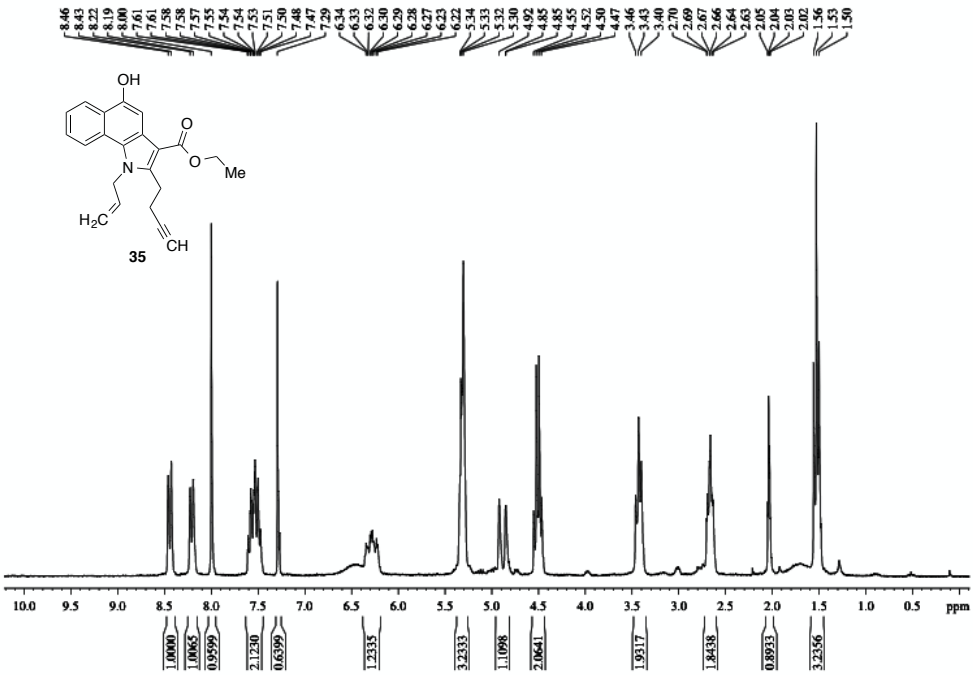
134.05
130.79
130.08
129.11
128.25
126.42
125.22
124.46
123.30
122.85
122.55
121.03
114.09
105.49
77.95
77.44
76.93
60.12
44.33
28.84
23.09
15.04
33
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.43
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8.00
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7.61
7.58
7.58
7.57
7.55
7.54
7.54
7.53
7.51
7.50
7.48
7.47
7.29
6.34
6.33
6.32
6.30
6.29
6.28
6.27
6.23
6.22
5.34
5.33
5.32
5.30
4.92
4.85
4.85
4.55
4.52
4.50
4.47
3.46
3.43
3.40
2.70
2.69
2.67
2.66
2.64
2.63
2.05
2.04
2.03
2.02
1.56
1.53
1.50
OH
O
O
Me
N
H2C
CH
35
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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1.0065
0.9599
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1.9317
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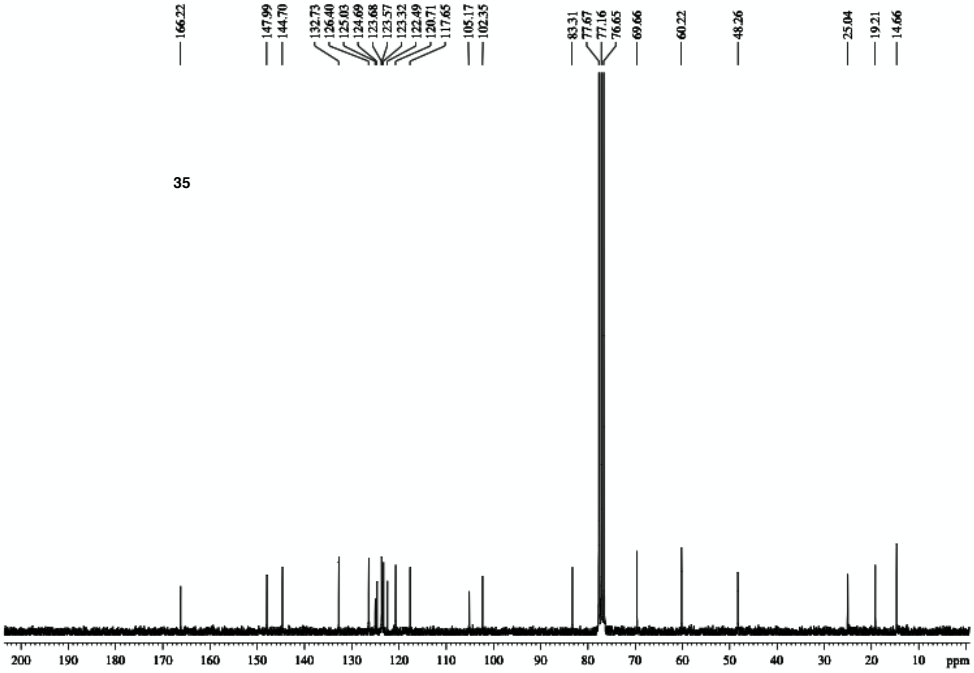
3.2356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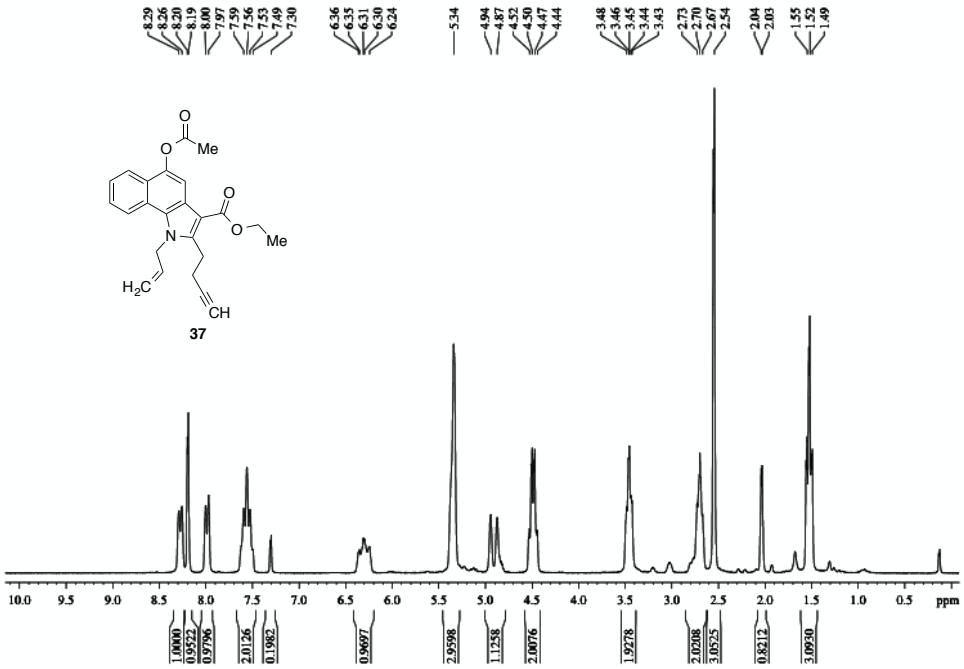
123.68
123.57
123.32
122.49
120.71
117.65
105.17
102.35
83.31
77.67
77.16
76.65
69.66
60.22
48.26
25.04
19.21
14.66
35
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.49
7.30
6.36
6.35
6.31
6.30
6.24
5.34
4.94
4.87
4.52
4.50
4.47
4.44
3.48
3.46
3.45
3.44
3.43
2.73
2.70
2.67
2.54
2.04
2.03
1.55
1.52
1.49
O
Me
O
O
O
Me
N
H2C
CH
37
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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0.9522
0.9796
2.0126
0.1982
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2.0208
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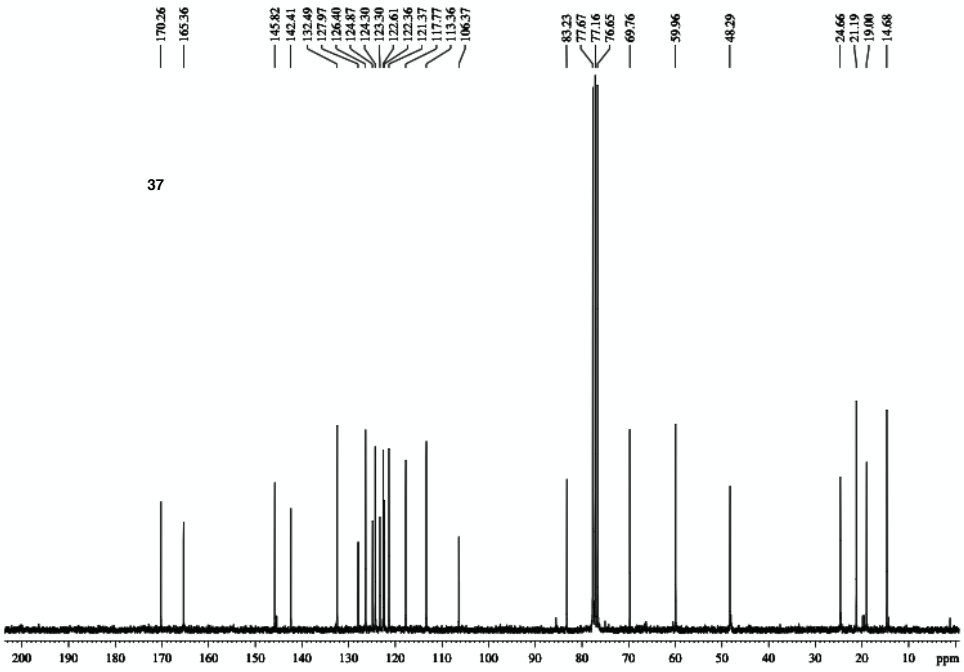
0.8212
3.0930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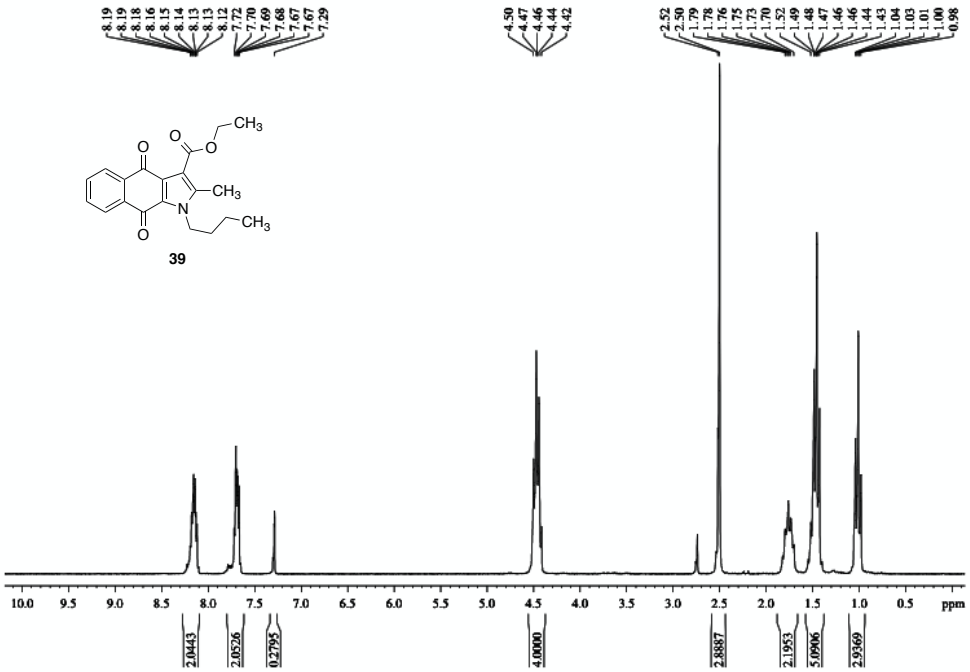
127.97
126.40
124.87
124.30
123.30
122.61
122.36
121.37
117.77
113.36
106.37
83.23
77.67
77.16
76.65
69.76
59.96
48.29
24.66
21.19
19.00
14.68
37
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.19
8.18
8.16
8.15
8.14
8.13
8.13
8.12
7.72
7.70
7.69
7.68
7.67
7.67
7.29
4.50
4.47
4.46
4.44
4.42
2.52
2.50
1.79
1.78
1.76
1.75
1.73
1.70
1.52
1.49
1.48
1.47
1.46
1.46
1.44
1.43
1.04
1.03
1.01
1.00
0.98
CH3
O
O
O
CH3
N
CH3
O
39
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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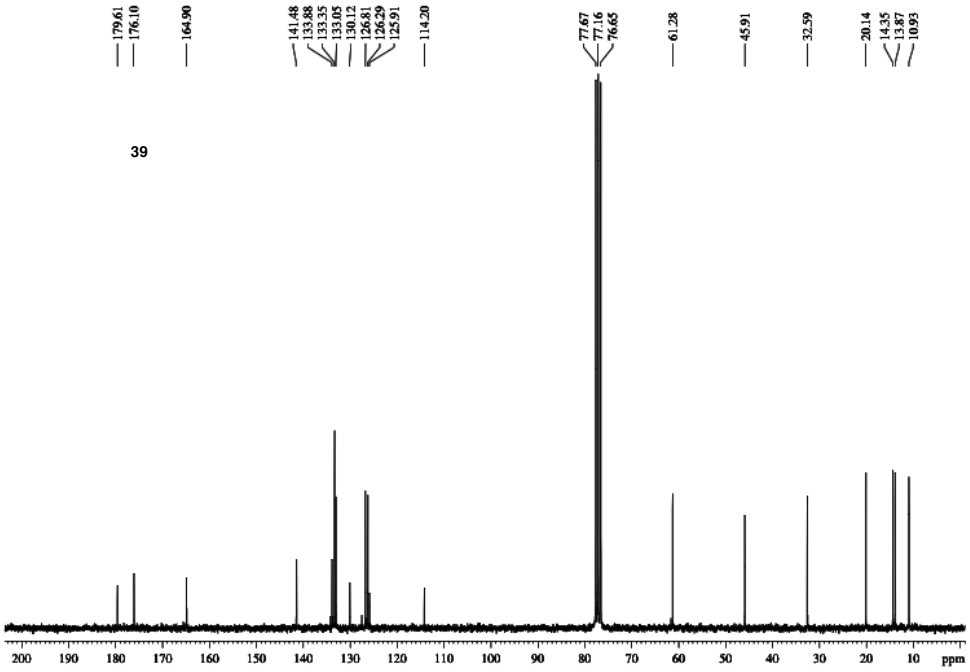
2.9369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133.05
130.12
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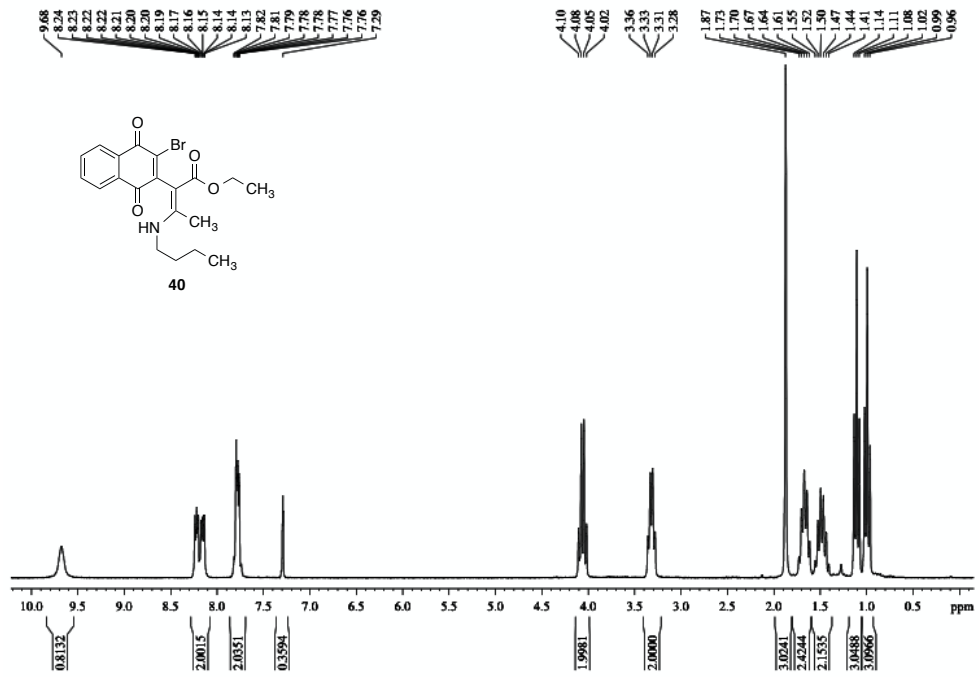
126.29
125.91
114.20
77.67
77.16
76.65
61.28
45.91
32.59
20.14
14.35
13.87
10.93
39
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.20
8.19
8.17
8.16
8.15
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8.14
8.13
7.82
7.81
7.79
7.78
7.78
7.77
7.77
7.76
7.76
7.29
4.10
4.08
4.05
4.02
3.36
3.33
3.31
3.28
1.87
1.73
1.70
1.67
1.64
1.61
1.55
1.52
1.50
1.47
1.44
1.41
1.14
1.11
1.08
1.02
0.99
0.96
O
Br
O
O
CH3
O
HN
CH3
CH3
40
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8132
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0.3594
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2.0000
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2.4344
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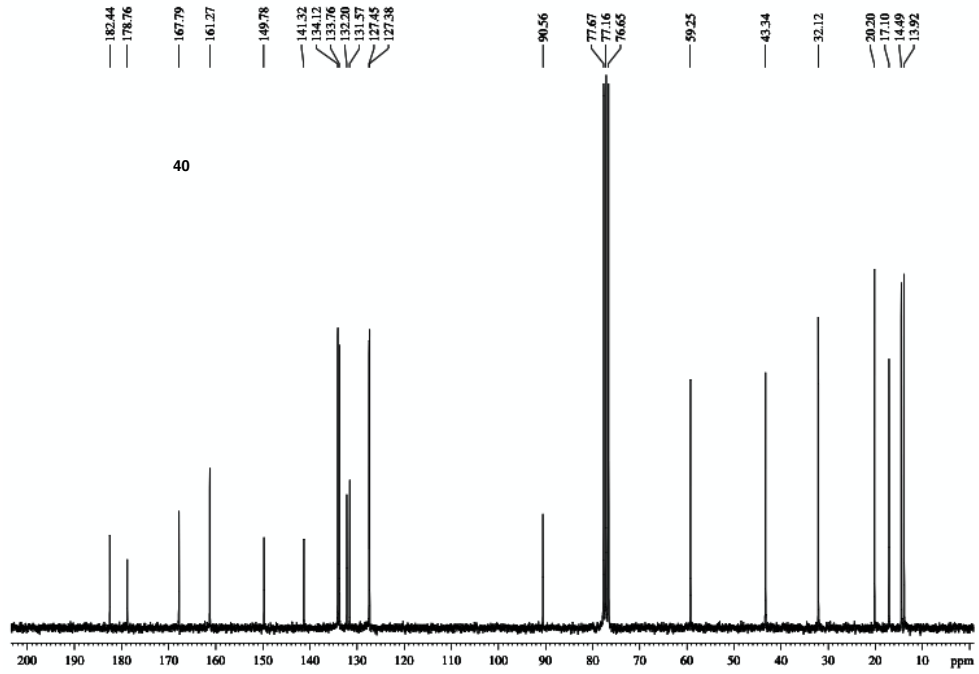
3.0966


182.44
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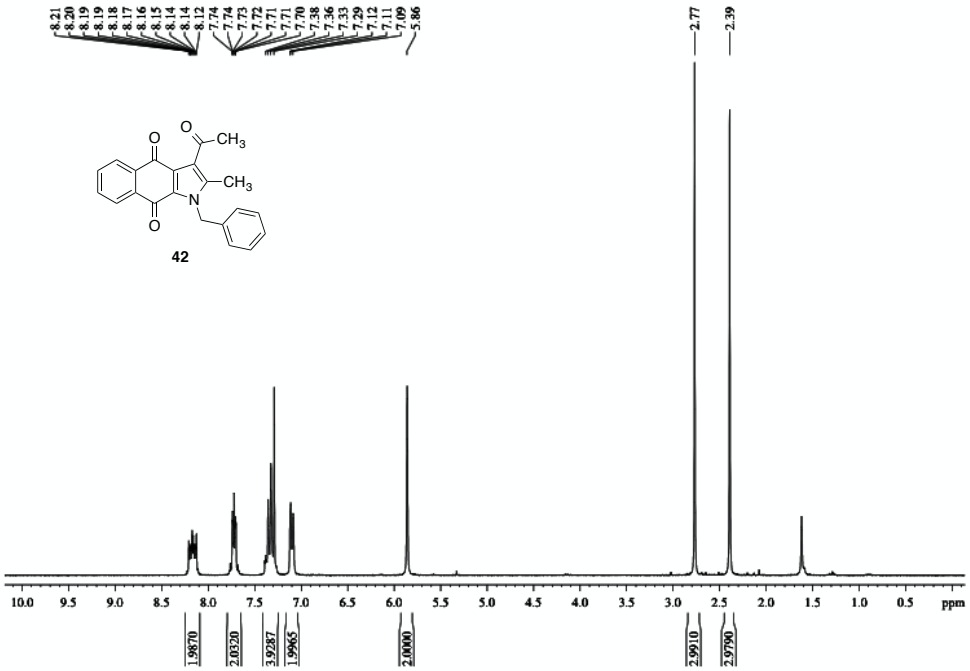
167.79
161.27
149.78
141.32
134.12
133.76
132.20
131.57
127.45
127.38
90.56
77.67
77.16
76.65
59.25
43.34
32.12
20.20
17.10
14.49
13.92
40
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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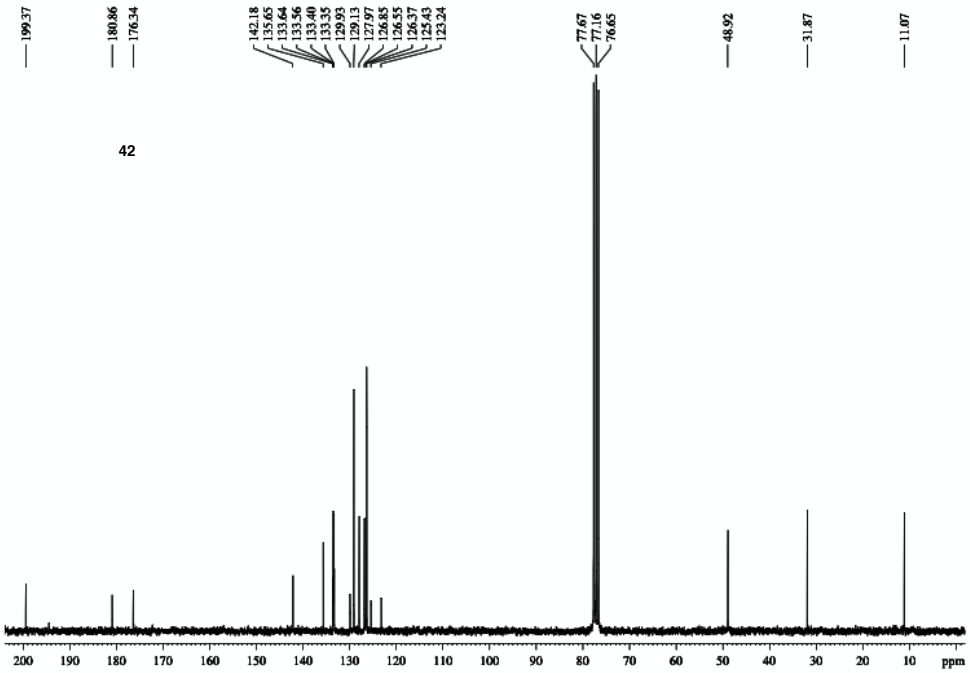
8.20
8.19
8.19
8.18
8.17
8.16
8.15
8.14
8.14
8.12
7.74
7.74
7.73
7.72
7.71
7.71
7.70
7.38
7.36
7.33
7.29
7.12
7.11
7.09
5.86
2.77
2.39
O
CH3
O
CH3
N
O
42
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.9870
2.0320
3.9287
1.9965
2.0000
2.9910
2.9790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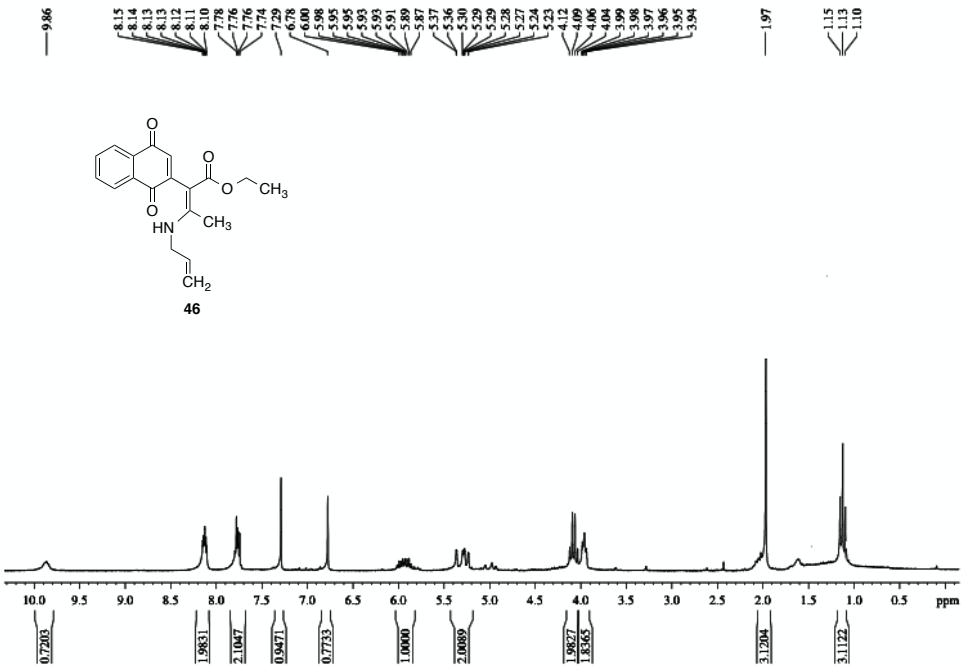
180.86
176.34
142.18
135.65
133.64
133.56
133.40
133.35
129.93
129.13
127.97
126.85
126.55
126.37
125.43
123.24
77.67
77.16
76.65
48.92
31.87
11.07
42
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.15
8.14
8.13
8.13
8.12
8.11
8.10
7.78
7.76
7.76
7.74
7.29
6.78
6.00
5.98
5.95
5.95
5.93
5.93
5.91
5.89
5.87
5.37
5.36
5.30
5.29
5.29
5.28
5.27
5.24
5.23
4.12
4.09
4.06
4.04
3.99
3.98
3.97
3.96
3.95
3.94
1.97
1.15
1.13
1.10
O
O
O
O
CH3
HN
CH3
CH2
46
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.7203
1.9831
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0.9471
0.7733
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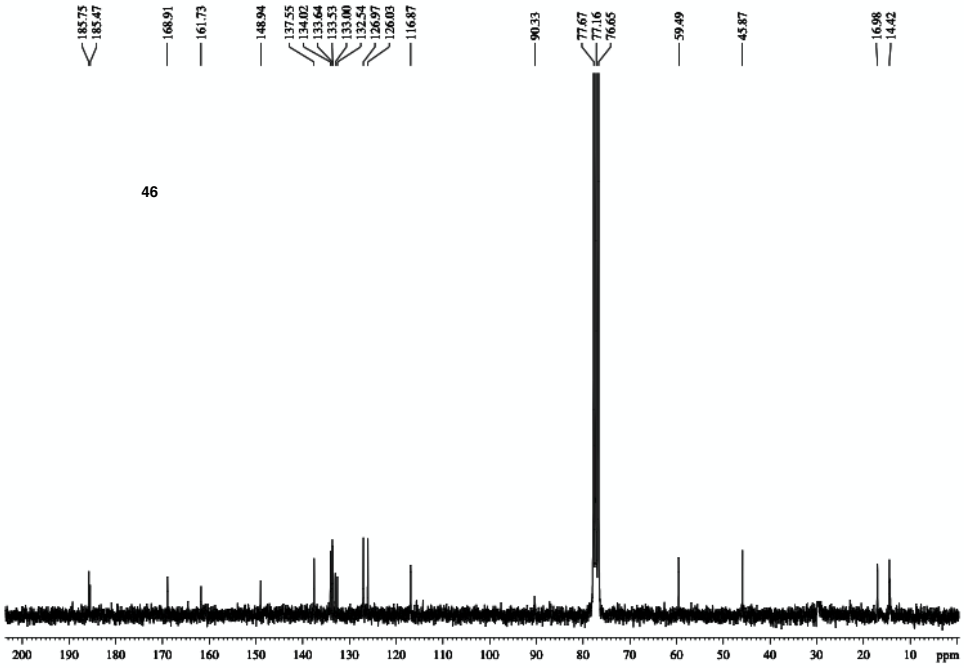
2.0089
1.9827
1.8365
3.1204
3.1122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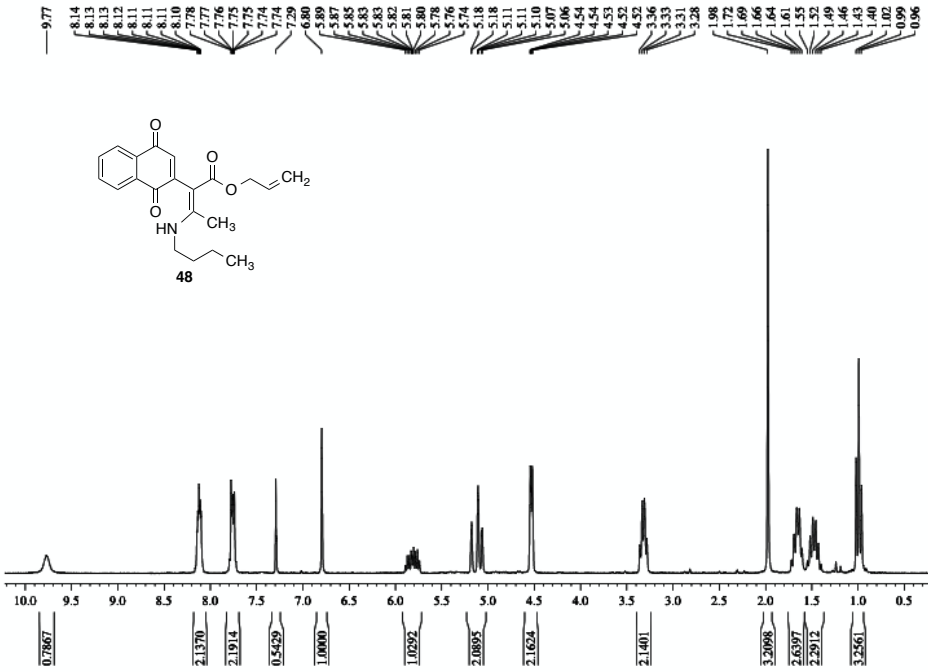
185.47
168.91
161.73
148.94
137.55
134.02
133.64
133.53
133.00
132.54
126.97
126.03
116.87
90.33
77.67
77.16
76.65
59.49
45.87
16.98
14.42
46
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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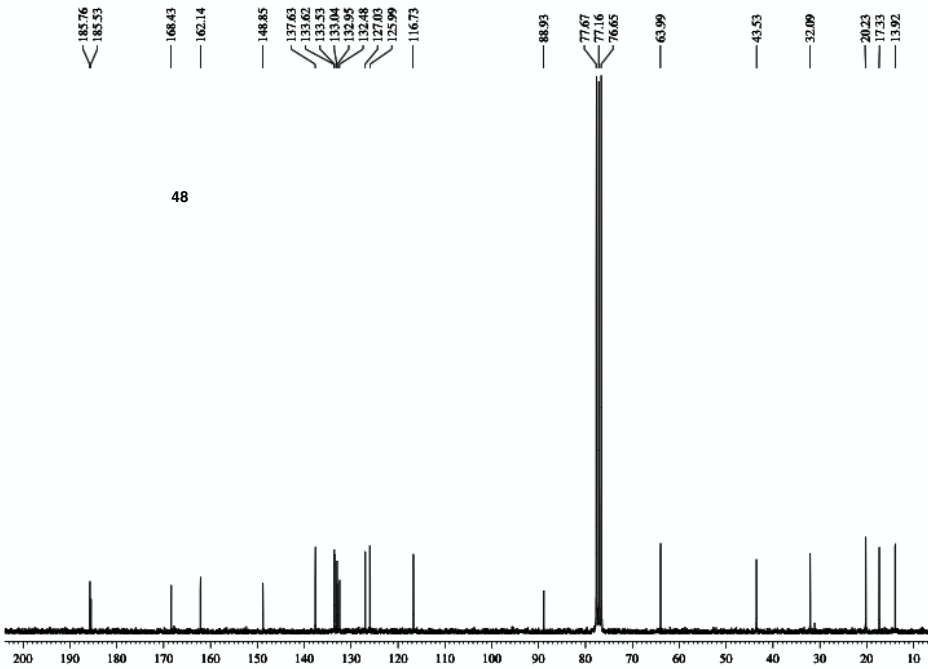
8.14
8.13
8.13
8.12
8.11
8.11
8.11
8.10
7.78
7.77
7.76
7.75
7.75
7.74
7.74
7.29
6.80
5.89
5.87
5.85
5.83
5.82
5.81
5.80
5.78
5.76
5.74
5.18
5.18
5.11
5.11
5.10
5.07
5.06
4.54
4.54
4.53
4.52
4.52
3.36
3.33
3.31
3.28
1.98
1.72
1.69
1.66
1.64
1.61
1.55
1.52
1.49
1.46
1.43
1.40
1.02
0.99
0.96
O
O
O
O
CH2
HN
CH3
CH3
48
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.7867
2.1370
2.1914
0.5429
1.0000
1.0292
2.0895
2.1624
2.1401
3.2098
2.6397
2.2912
3.2561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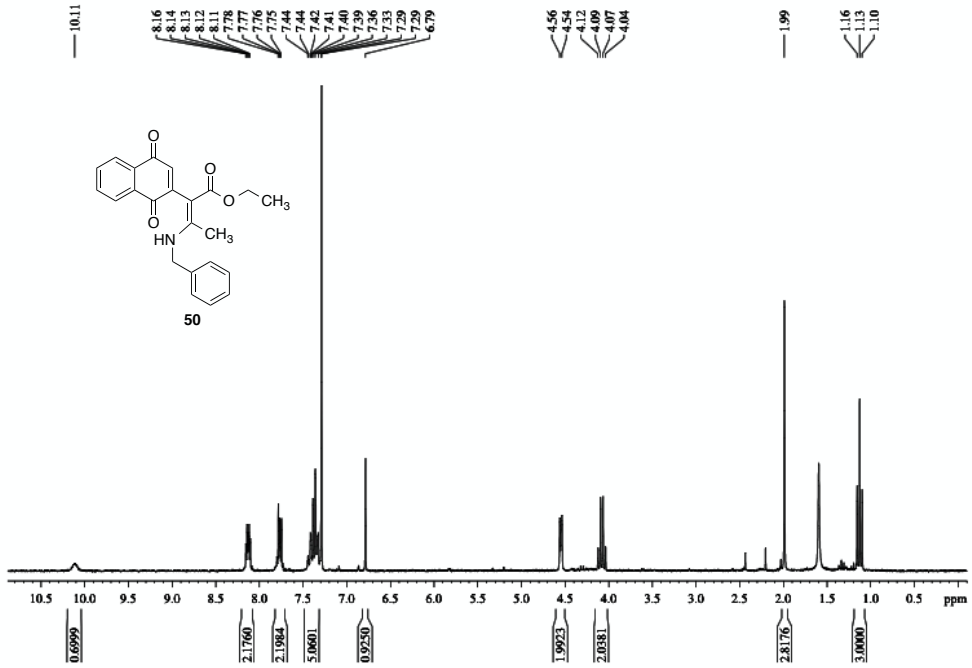
185.53
168.43
162.14
148.85
137.63
133.62
133.53
133.04
132.95
132.48
127.03
125.99
116.73
88.93
77.67
77.16
76.65
63.99
43.53
32.09
20.23
17.33
13.92
48
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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8.16
8.14
8.13
8.12
8.11
7.78
7.77
7.76
7.75
7.44
7.42
7.41
7.40
7.39
7.36
7.33
7.29
7.29
6.79
4.56
4.54
4.12
4.09
4.07
4.04
1.99
1.16
1.13
1.10
O
O
O
O
CH3
HN
CH3
50
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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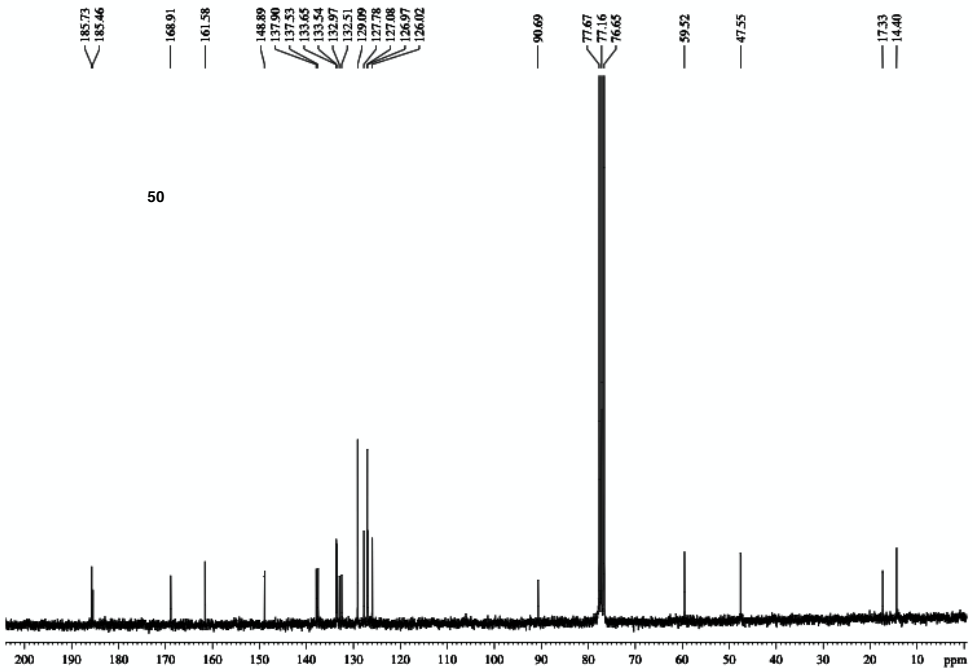
2.1760
2.1984
5.0601
0.9250
1.9923
2.0381
2.8176
3.0000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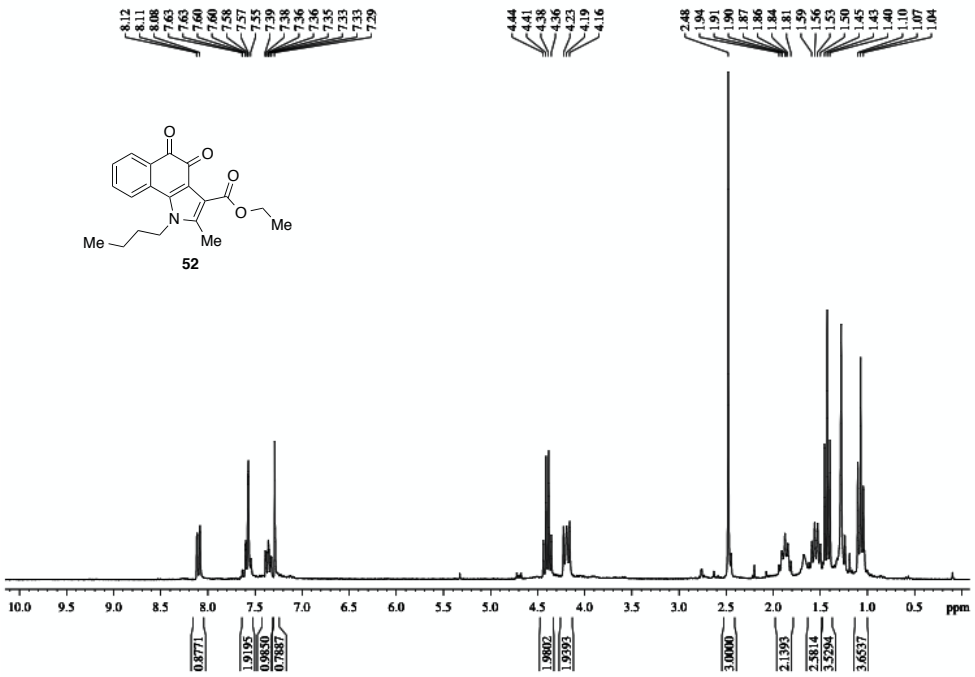
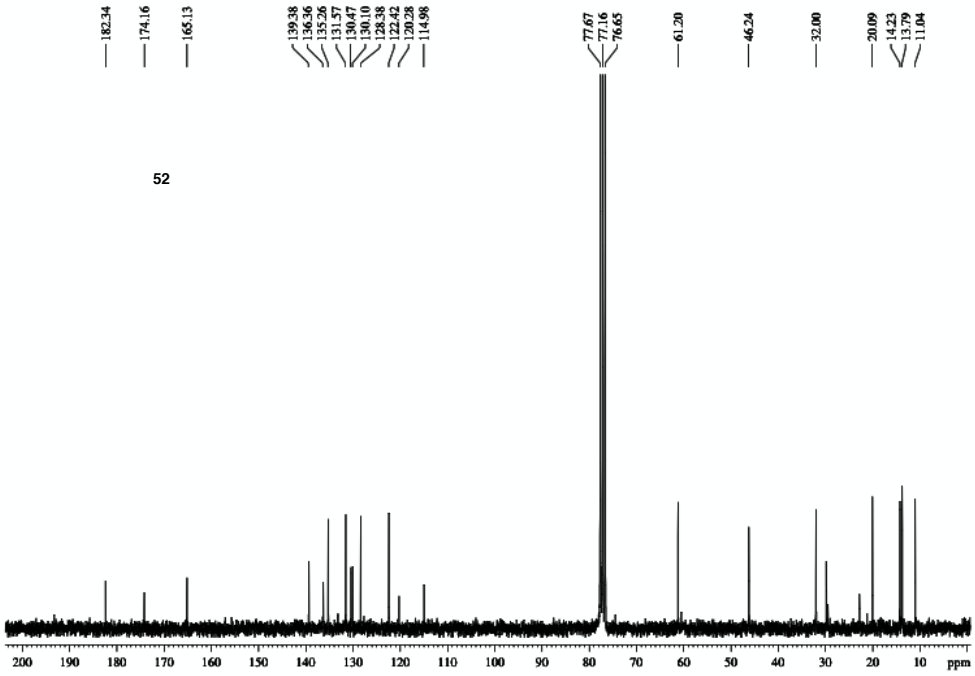
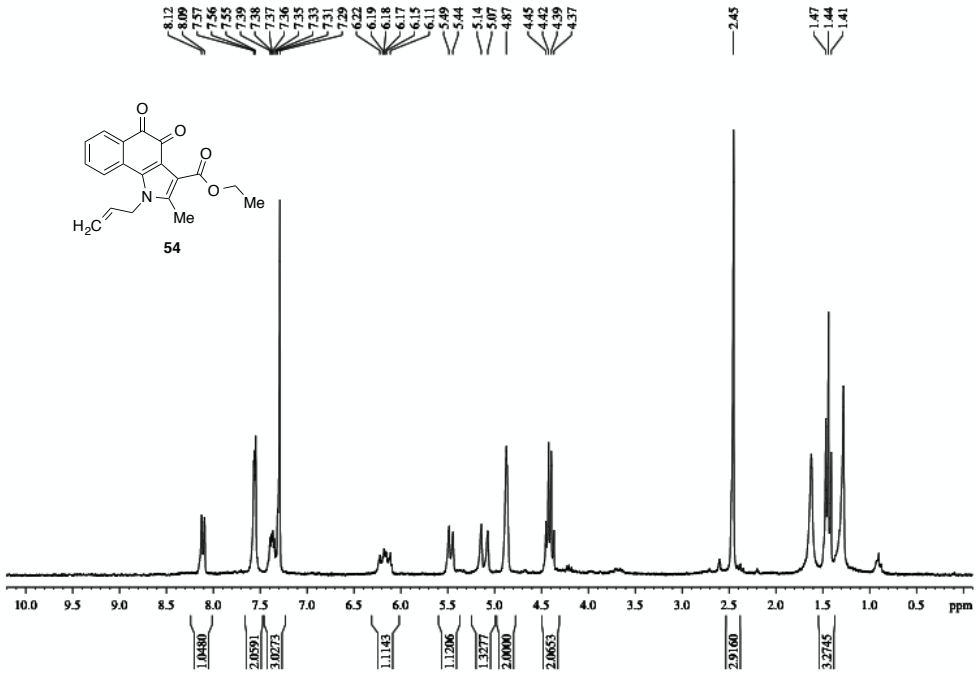
185.46
168.91
161.58
148.89
137.90
137.53
133.65
133.54
132.97
132.51
129.09
127.78
127.08
126.97
126.02
90.69
77.67
77.16
76.65
59.52
47.55
17.33
14.40
50
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.12
8.11
8.08
7.63
7.63
7.60
7.60
7.58
7.57
7.55
7.39
7.38
7.36
7.36
7.35
7.33
7.33
7.29
4.44
4.41
4.38
4.36
4.23
4.19
4.16
2.48
1.94
1.91
1.90
1.87
1.86
1.84
1.81
1.59
1.56
1.53
1.50
1.45
1.43
1.40
1.10
1.07
1.04
O
O
O
O
N
Me
Me
Me
52
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8771
1.9195
0.9850
0.7887
1.9802
1.9393
3.0000
2.1393
2.5814
3.5294
3.6537


182.34
174.16
165.13
139.38
136.36
135.26
131.57
130.47
130.10
128.38
122.42
120.28
114.98
77.67
77.16
76.65
61.20
46.24
32.00
20.09
14.23
13.79
11.04
52
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.09
7.57
7.56
7.55
7.39
7.38
7.37
7.36
7.35
7.33
7.31
7.29
6.22
6.19
6.18
6.17
6.15
6.11
5.49
5.44
5.14
5.07
4.87
4.45
4.42
4.39
4.37
2.45
1.47
1.44
1.41
O
O
O
O
N
Me
Me
H2C
54
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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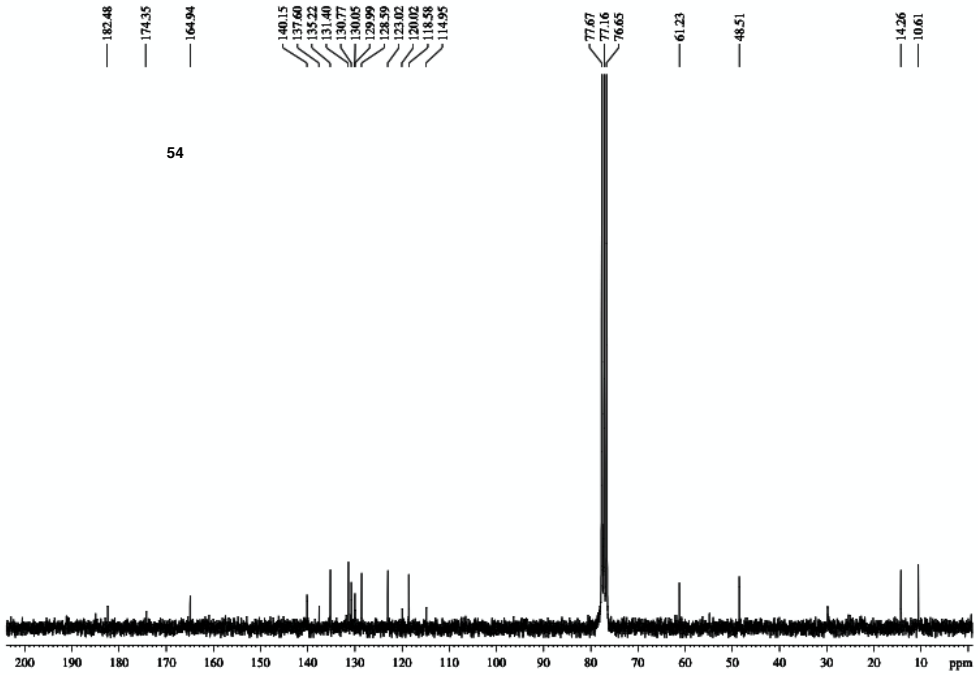
3.0273
1.1143
1.1206
1.3277
2.0000
2.0653
2.9160
3.2745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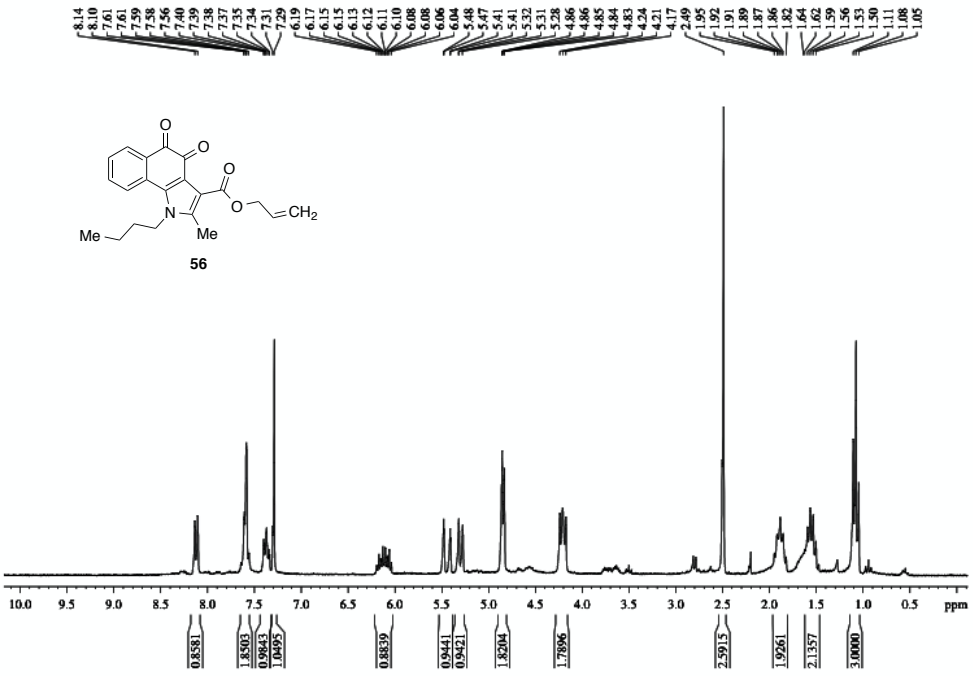
174.35
164.94
140.15
137.60
135.22
131.40
130.77
130.05
129.99
128.59
123.02
120.02
118.58
114.95
77.67
77.16
76.65
61.23
48.51
14.26
10.61
54
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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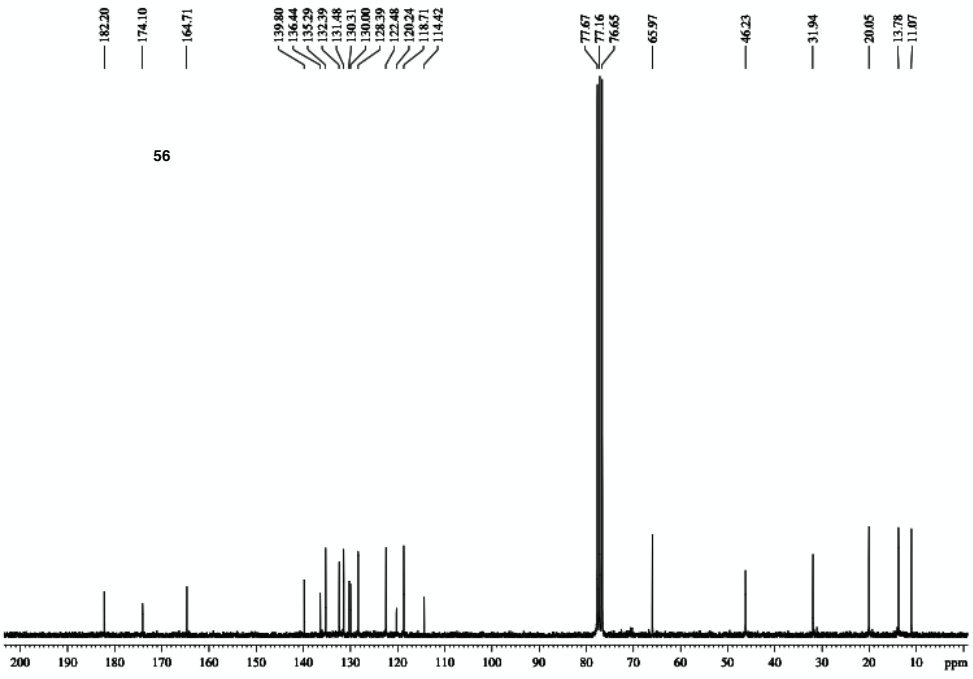
8.10
7.61
7.61
7.59
7.58
7.56
7.40
7.39
7.38
7.37
7.35
7.34
7.31
7.29
6.19
6.17
6.15
6.15
6.13
6.12
6.11
6.10
6.08
6.08
6.06
6.04
5.48
5.47
5.41
5.41
5.32
5.31
5.28
4.86
4.86
4.85
4.84
4.83
4.24
4.21
4.17
2.49
1.95
1.92
1.91
1.89
1.87
1.86
1.82
1.64
1.62
1.59
1.56
1.53
1.50
1.11
1.08
1.05
O
O
O
O
N
Me
Me
CH2
56
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8581
1.8503
0.9843
1.0495
0.8839
0.9441
0.9421
1.8204
1.7896
2.5915
1.9261
2.1357
3.0000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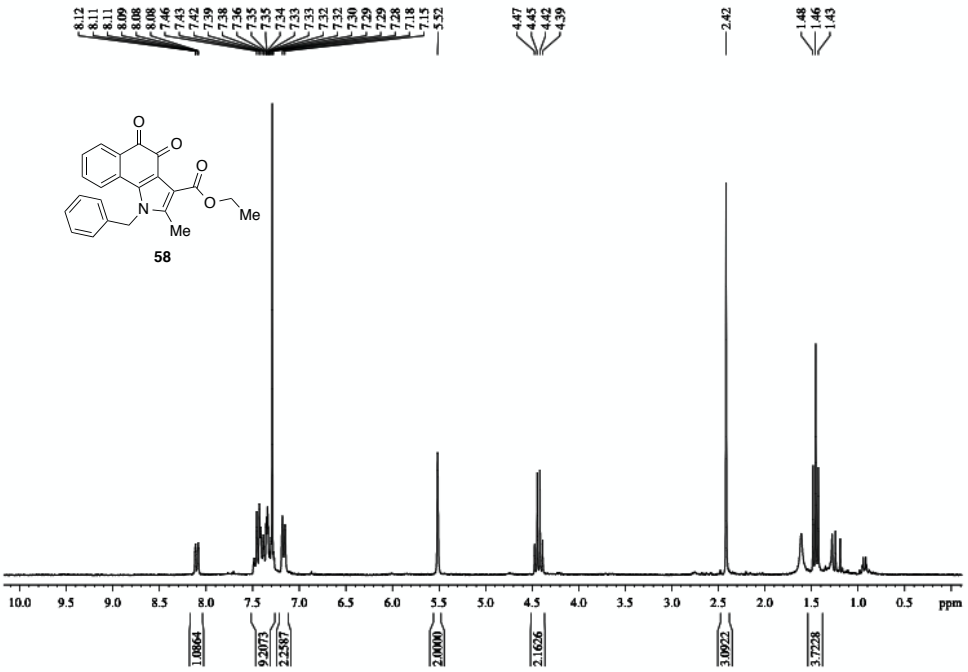
132.39
131.48
130.31
130.00
128.39
122.48
120.24
118.71
114.42
77.67
77.16
76.65
65.97
46.23
31.94
20.05
13.78
11.07
56
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.12
8.11
8.11
8.09
8.09
8.08
8.08
7.46
7.43
7.42
7.39
7.38
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.30
7.29
7.29
7.28
7.18
7.15
5.52
4.47
4.45
4.42
4.39
2.42
1.48
1.46
1.43
O
O
O
O
N
Me
Me
58
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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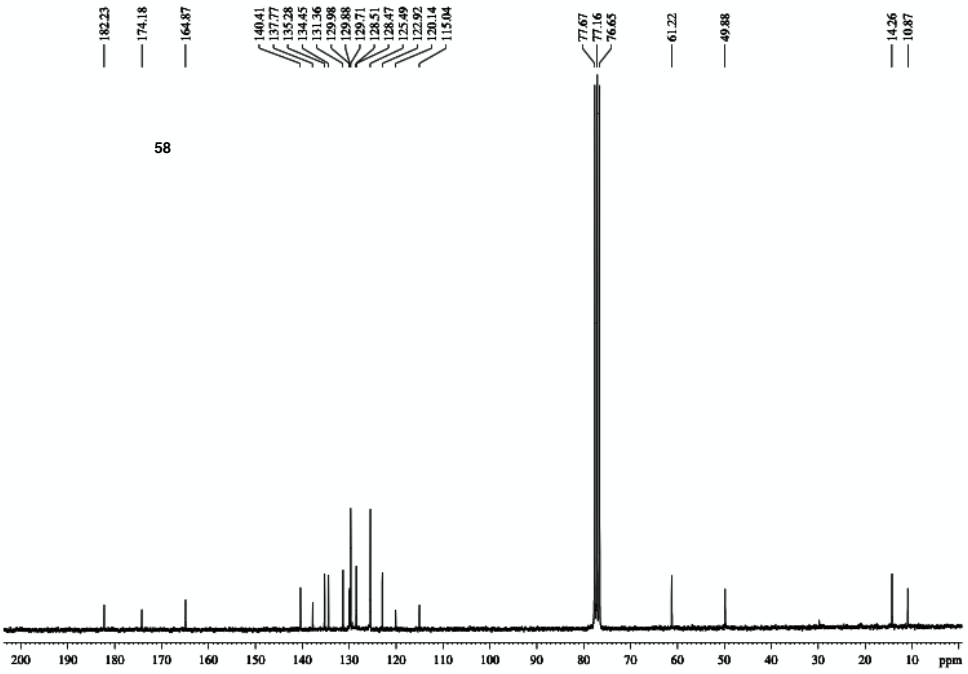
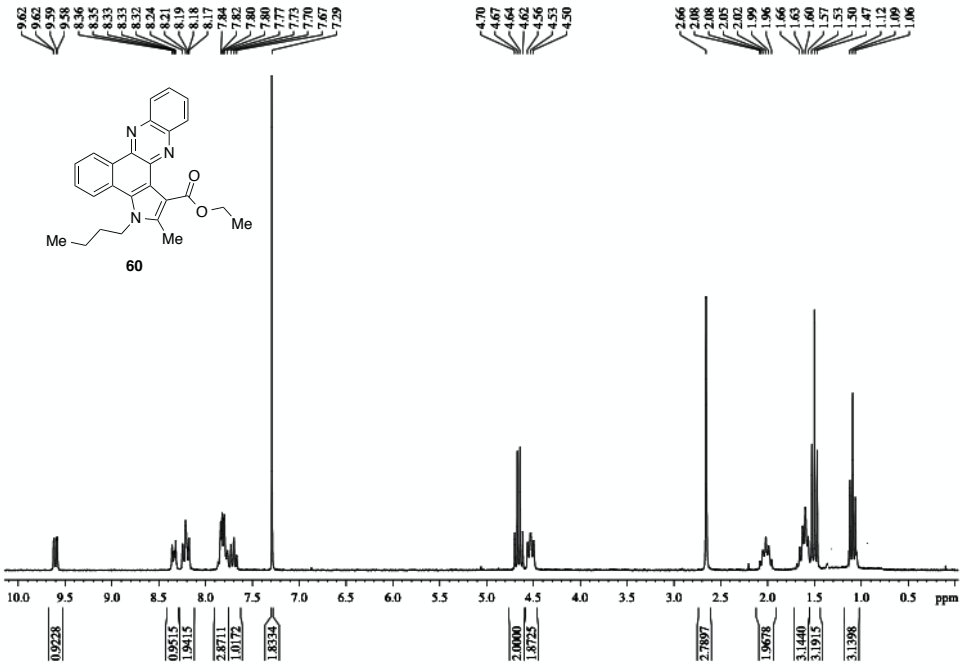
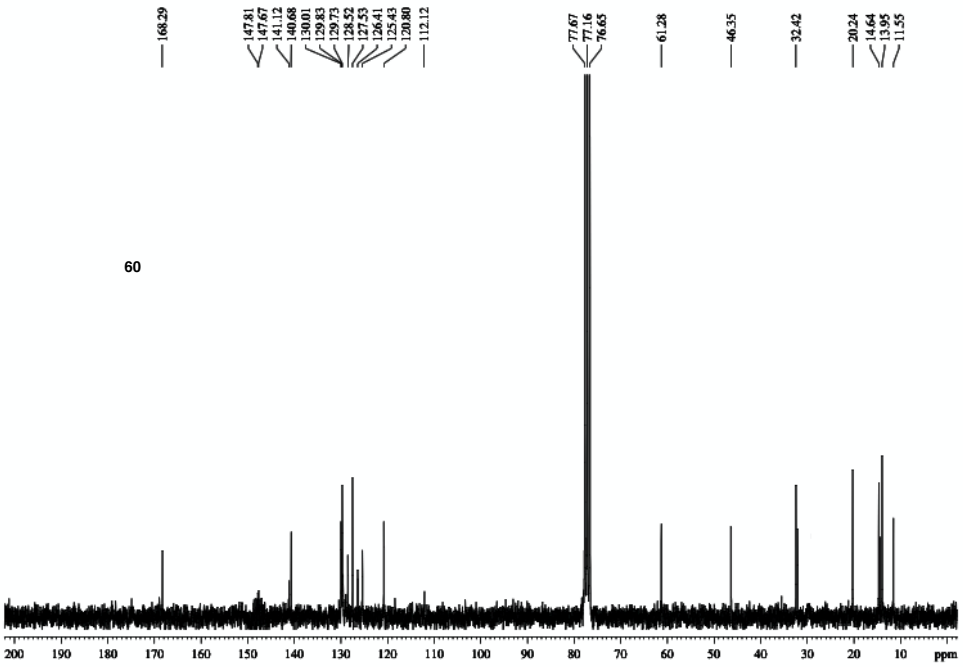
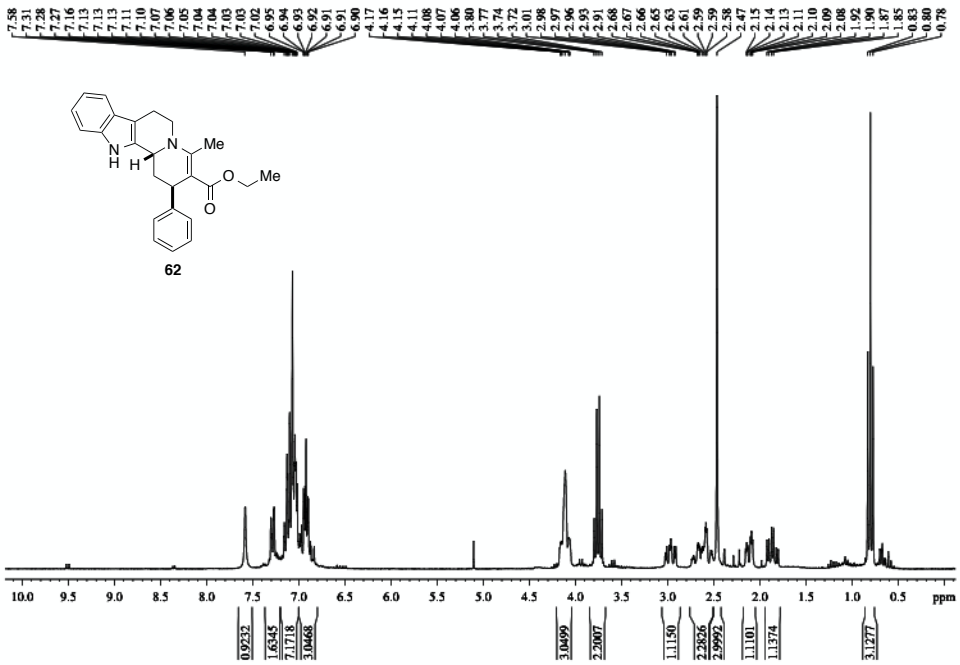
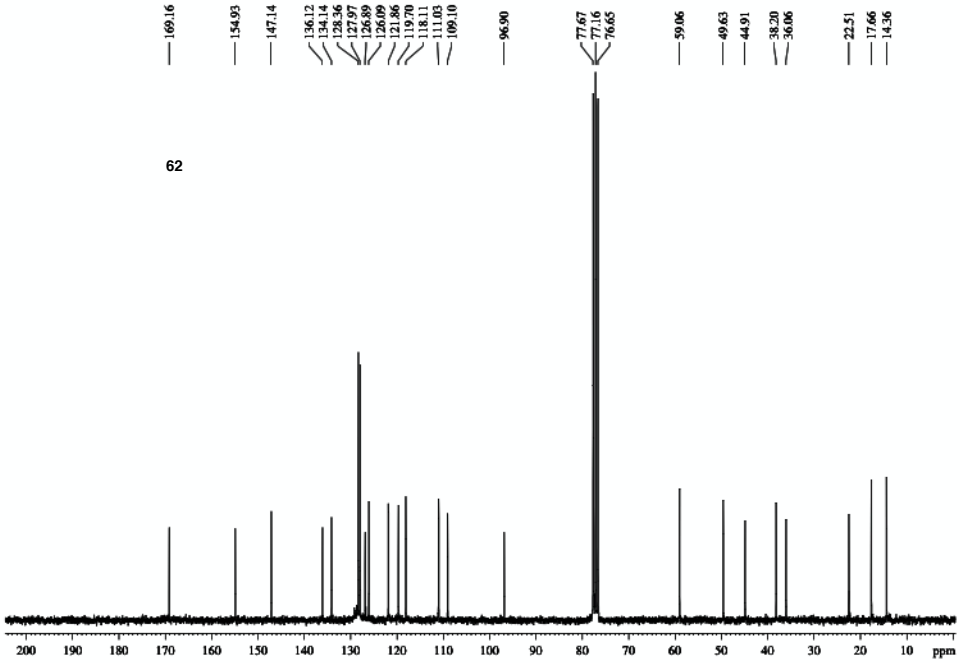
9.2073
2.2587
2.0000
2.1626
3.0922
3.7228

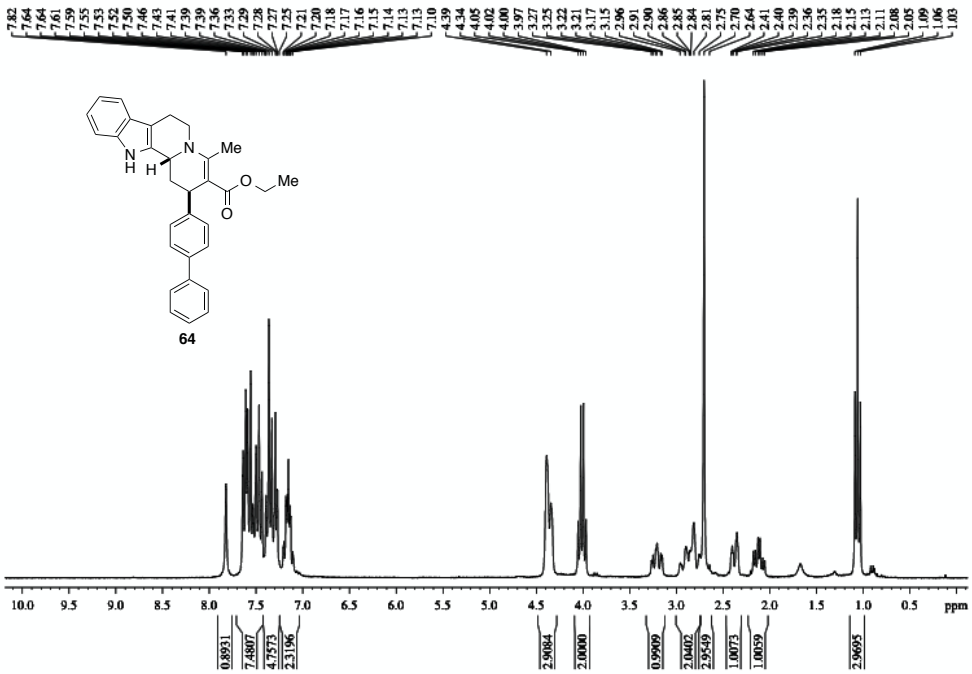

182.23
174.18
164.87
140.41
137.77
135.28
134.45
131.36
129.98
129.88
129.71
128.51
128.47
125.49
122.92
120.14
115.04
77.67
77.16
76.65
61.22
49.88
14.26
10.87
58
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

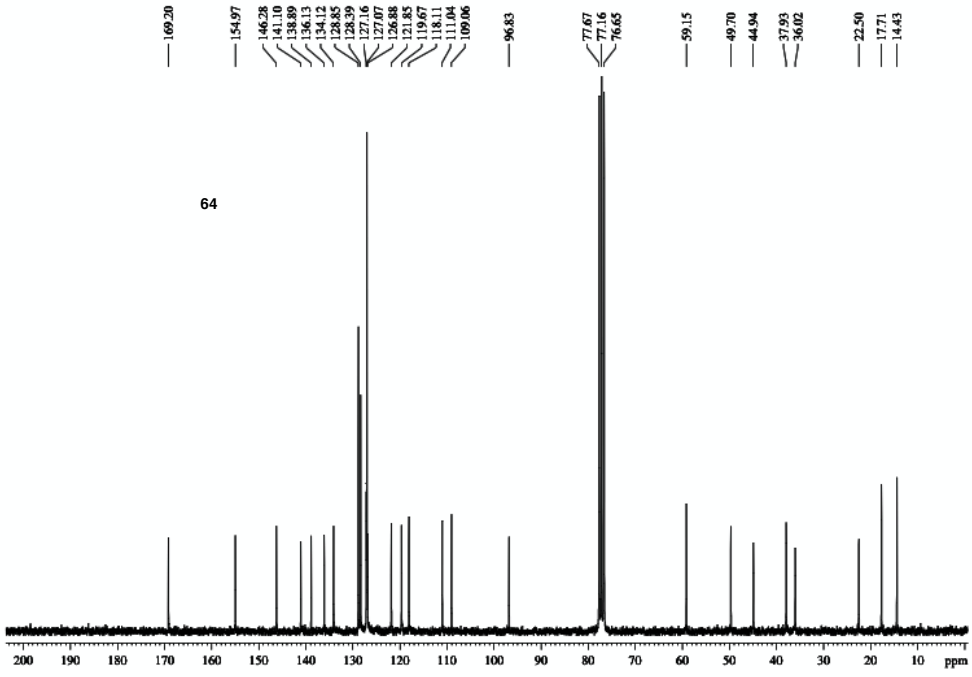

9.62
9.62
9.59
9.58
8.36
8.35
8.33
8.33
8.32
8.24
8.21
8.19
8.18
8.17
7.84
7.82
7.80
7.80
7.77
7.73
7.70
7.67
7.29
4.70
4.67
4.64
4.62
4.56
4.53
4.50
2.66
2.08
2.08
2.05
2.02
1.99
1.96
1.66
1.63
1.60
1.57
1.53
1.50
1.47
1.12
1.09
1.06
N
N
O
O
N
Me
Me
Me
60
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.9228
0.9515
1.9415
2.8711
1.0172
1.8334
2.0000
1.8725
2.7897
1.9678
3.1440
3.1915
3.1398

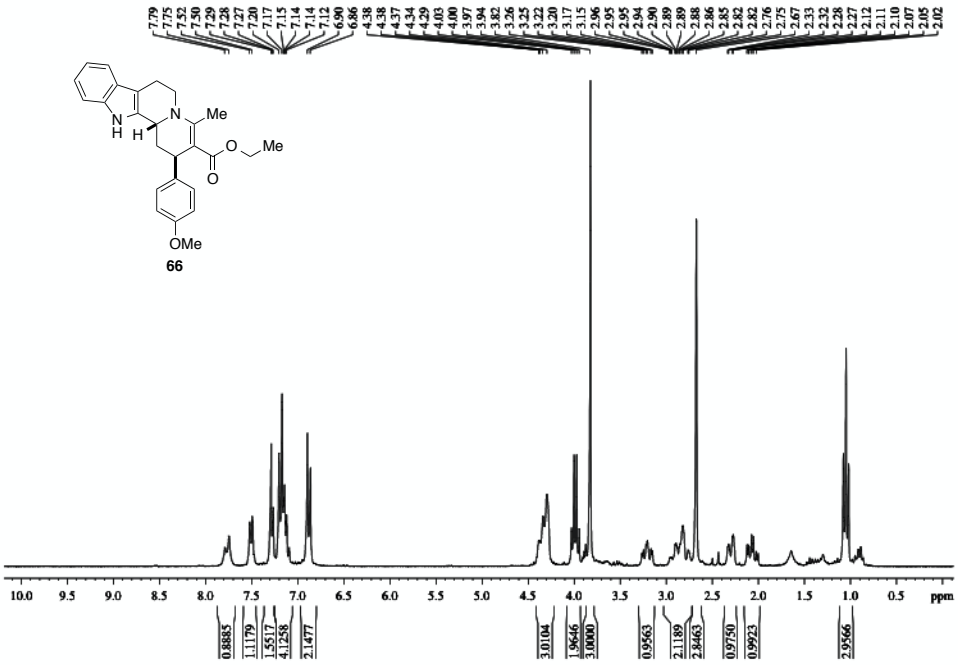

160.29
147.81
147.67
141.12
140.68
130.01
129.83
129.73
128.52
127.53
126.41
125.43
120.80
112.12
77.67
77.16
76.65
61.28
46.35
32.42
20.24
14.64
13.95
11.55
60
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

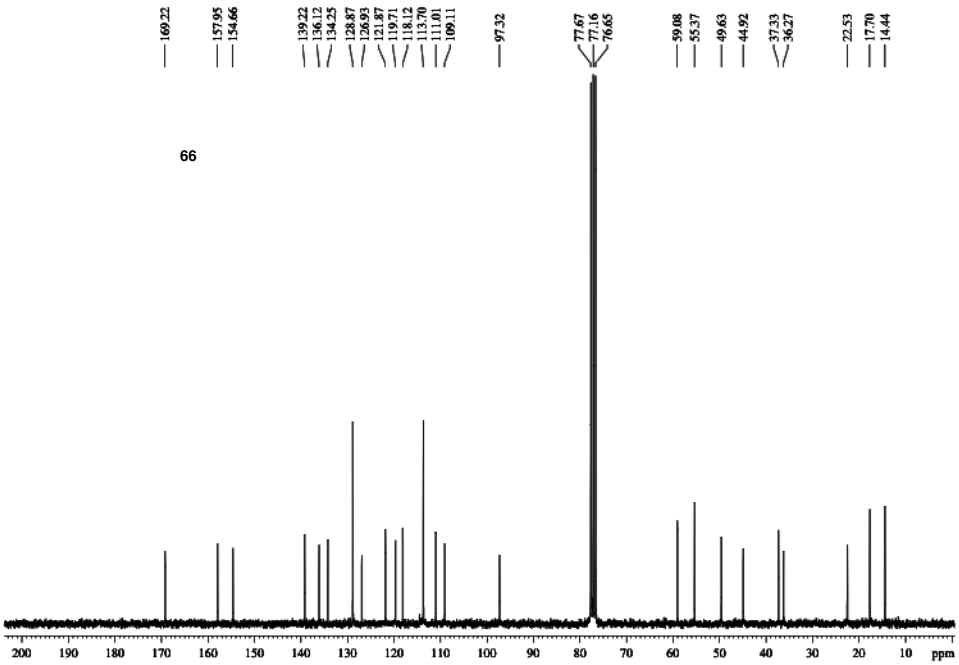

7.58 7.31 7.28 7.27 7.16 7.13 7.13 7.11 7.10 7.07 7.06 7.05 7.04 7.04 7.03 7.03 7.02 6.95 6.94 6.93 6.92 6.91 6.91 6.90 4.17 4.16 4.15 4.11 4.08 4.07 4.06 3.80 3.77 3.74 3.72 3.01 2.98 2.97 2.96 2.93 2.91 2.68 2.67 2.66 2.65 2.63 2.61 2.59 2.59 2.58 2.47 2.15 2.14 2.13 2.11 2.10 2.09 2.08 1.92 1.90 1.87 1.85 0.83 0.80 0.78
N H H N Me O O Me
62
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.9232 1.6345 7.1718 3.0468 3.0499 2.2007 1.1150 2.2836 2.9992 1.1101 1.1374 3.1277

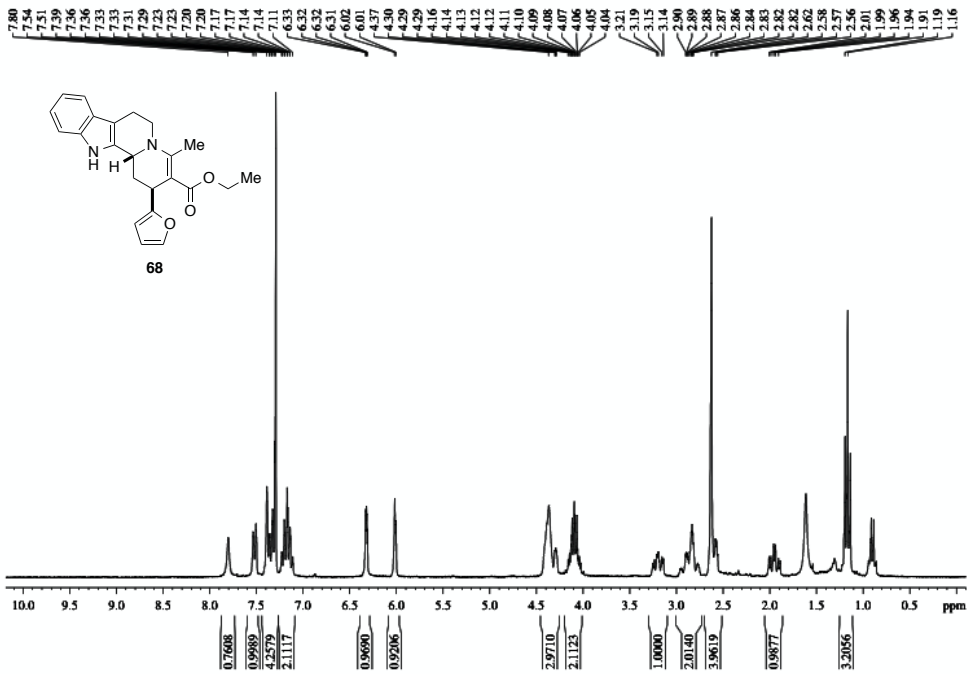

169.16 154.93 147.14 136.12 134.14 128.36 127.97 126.89 126.09 121.86 119.70 118.11 111.03 109.10 96.90 77.67 77.16 76.65 59.06 49.63 44.91 38.20 36.06 22.51 17.66 14.36
62
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

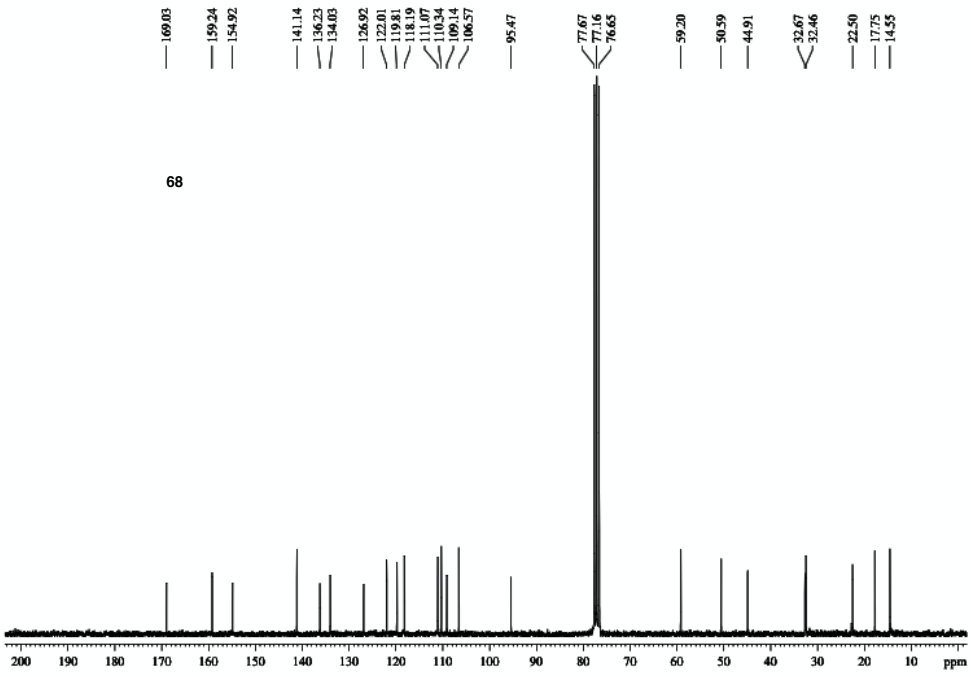

7.82 7.64 7.64 7.61 7.59 7.55 7.53 7.52 7.50 7.46 7.43 7.41 7.39 7.39 7.36 7.33 7.29 7.28 7.27 7.25 7.21 7.20 7.18 7.17 7.16 7.15 7.14 7.13 7.13 7.10 4.39 4.34 4.05 4.02 4.00 3.97 3.27 3.25 3.22 3.21 3.17 3.15 2.96 2.91 2.90 2.86 2.85 2.84 2.81 2.75 2.70 2.64 2.41 2.40 2.39 2.36 2.35 2.18 2.15 2.13 2.11 2.08 2.05 1.09 1.06 1.03
N
H
H
N
Me
O
Me
O
64
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8931 7.4807 4.7573 2.3196 2.9084 2.0000 0.9909 2.0402 2.9549 1.0073 1.0059 2.9695

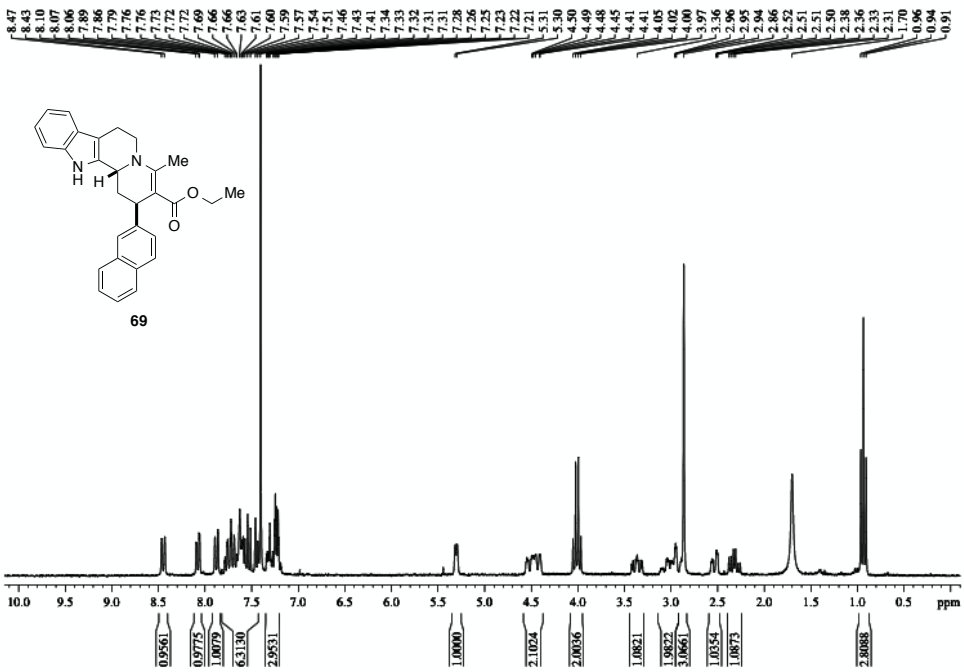

169.20 154.97 146.28 141.10 138.89 136.13 134.12 128.85 128.39 127.16 127.07 126.88 121.85 119.67 118.11 111.04 109.06 96.83 77.67 77.16 76.65 59.15 49.70 44.94 37.93 36.02 22.50 17.71 14.43
64
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

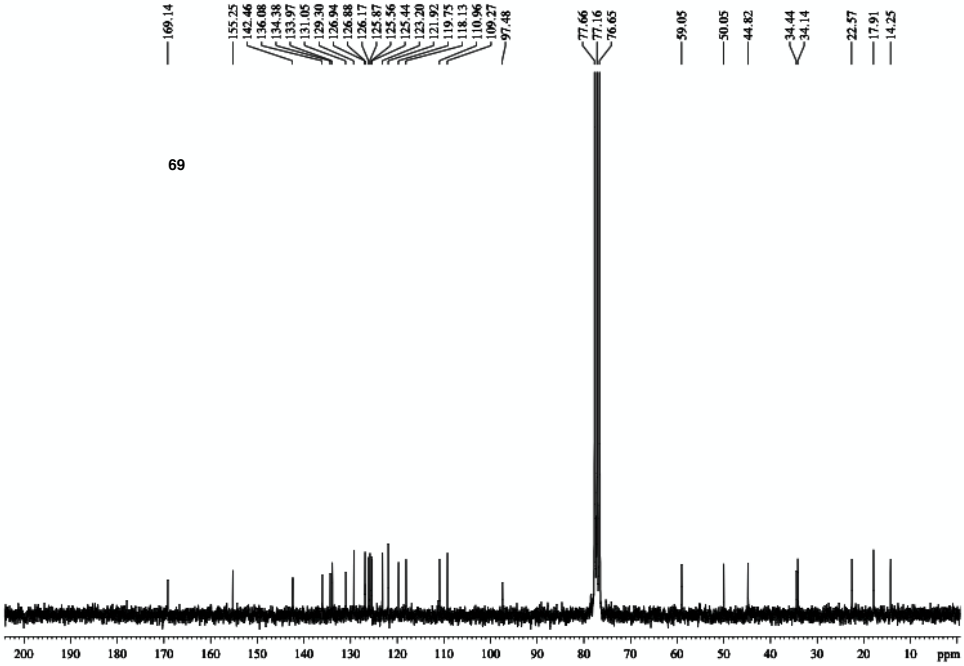

7.79 7.75 7.52 7.50 7.29 7.28 7.27 7.20 7.17 7.15 7.14 7.14 7.12 6.90 6.86 4.38 4.38 4.37 4.34 4.29 4.03 4.00 3.97 3.94 3.82 3.26 3.25 3.22 3.20 3.17 3.15 2.96 2.95 2.95 2.94 2.90 2.89 2.89 2.88 2.86 2.85 2.82 2.82 2.76 2.75 2.67 2.33 2.32 2.28 2.27 2.12 2.11 2.10 2.07 2.05 2.02
N
H
H
N
Me
O
Me
O
OMe
66
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8885 1.1179 1.5517 4.1258 2.1477 3.0104 1.9646 3.0000 0.9563 2.1189 2.8463 0.9750 0.9923 2.9566

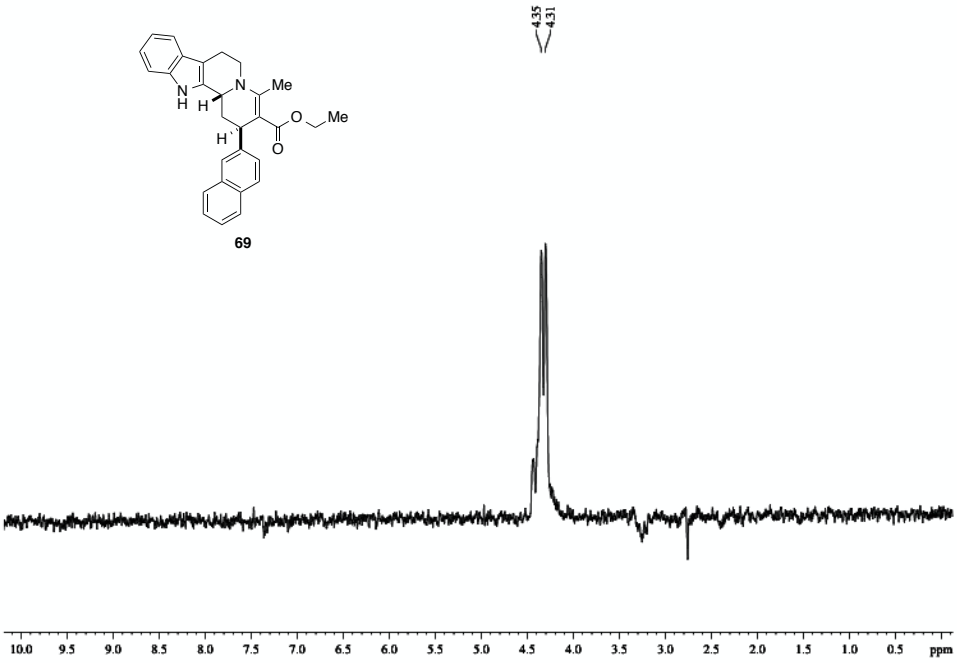

169.22 157.95 154.66 139.22 136.12 134.25 128.87 126.93 121.87 119.71 118.12 113.70 111.01 109.11 97.32 77.67 77.16 76.65 59.08 55.37 49.63 44.92 37.33 36.27 22.53 17.70 14.44
66
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.80
7.54
7.51
7.39
7.36
7.36
7.33
7.33
7.31
7.29
7.23
7.20
7.20
7.17
7.17
7.14
7.14
7.11
6.33
6.32
6.32
6.31
6.02
6.01
4.37
4.30
4.29
4.29
4.16
4.14
4.13
4.12
4.12
4.11
4.10
4.09
4.08
4.07
4.06
4.05
4.04
3.21
3.19
3.15
3.14
2.90
2.89
2.88
2.87
2.86
2.84
2.83
2.82
2.82
2.62
2.58
2.57
2.56
2.01
1.99
1.96
1.94
1.91
1.19
1.16
N
H
H
N
Me
O
O
Me
O
68
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.7608
0.9989
4.2579
2.1117
0.9690
0.9206
2.9710
2.1123
1.0000
2.0140
3.9619
0.9877
3.2056

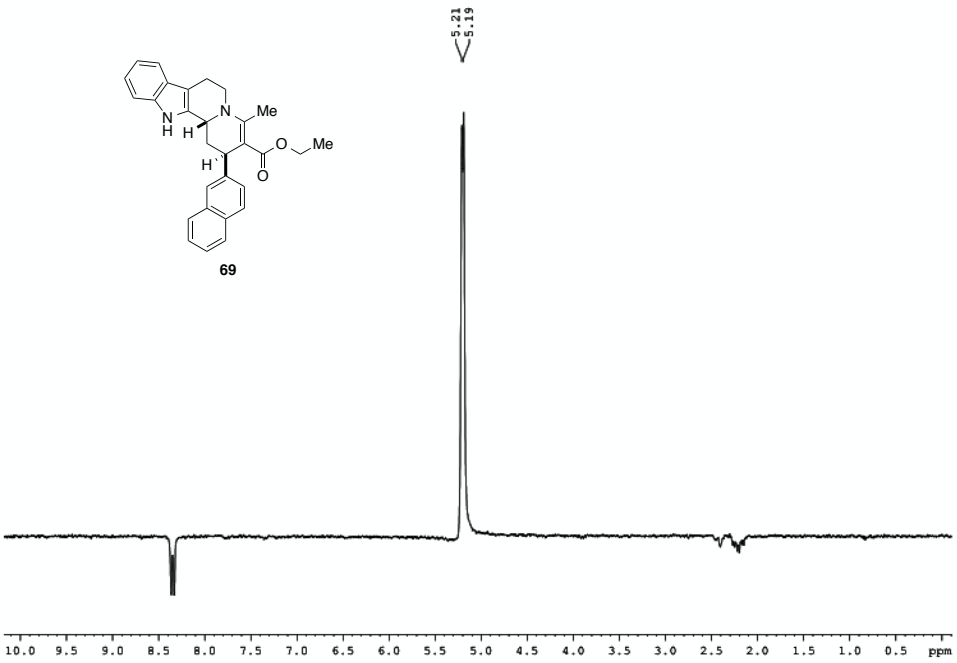

169.03
159.24
154.92
141.14
136.23
134.03
126.92
122.01
119.81
118.19
111.07
110.34
109.14
106.57
95.47
77.67
77.16
76.65
59.20
50.59
44.91
32.67
32.46
22.50
17.75
14.55
68
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


8.47 8.43 8.10 8.07 8.06 7.89 7.86 7.79 7.76 7.76 7.73 7.72 7.72 7.69 7.66 7.66 7.63 7.61 7.60 7.59 7.57 7.54 7.51 7.46 7.43 7.41 7.34 7.33 7.32 7.31 7.31 7.28 7.26 7.25 7.23 7.22 7.21 5.31 5.30 4.50 4.49 4.48 4.45 4.41 4.41 4.05 4.02 4.00 3.97 3.36 2.96 2.95 2.94 2.86 2.52 2.51 2.51 2.50 2.38 2.36 2.33 2.31 1.70 0.96 0.94 0.91
N
H
H
N
Me
O
Me
O
69
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.9561 0.9775 1.0079 6.3130 2.9531 1.0000 2.1024 2.0036 1.0821 1.9822 3.0661 1.0354 1.0873 2.8088

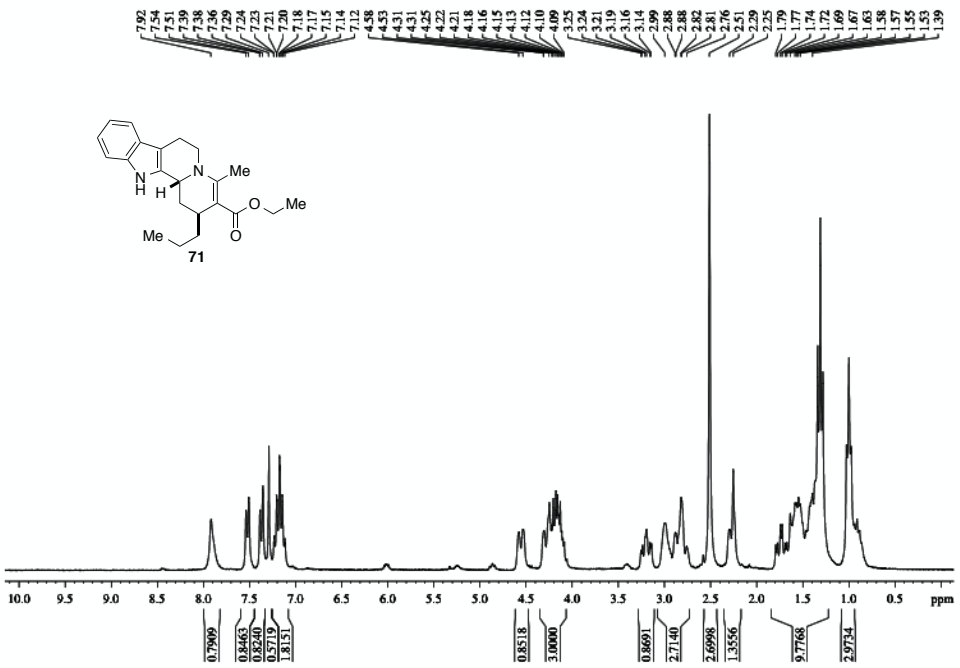

169.14
155.25 142.46 136.08 134.38 133.97 131.05 129.30 126.94 126.88 126.17 125.87 125.56 125.44 123.20 121.92 119.75 118.13 110.96 109.27 97.48
77.66 77.16 76.65
59.05
50.05
44.82
34.44 34.14
22.57
17.91
14.25
69
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

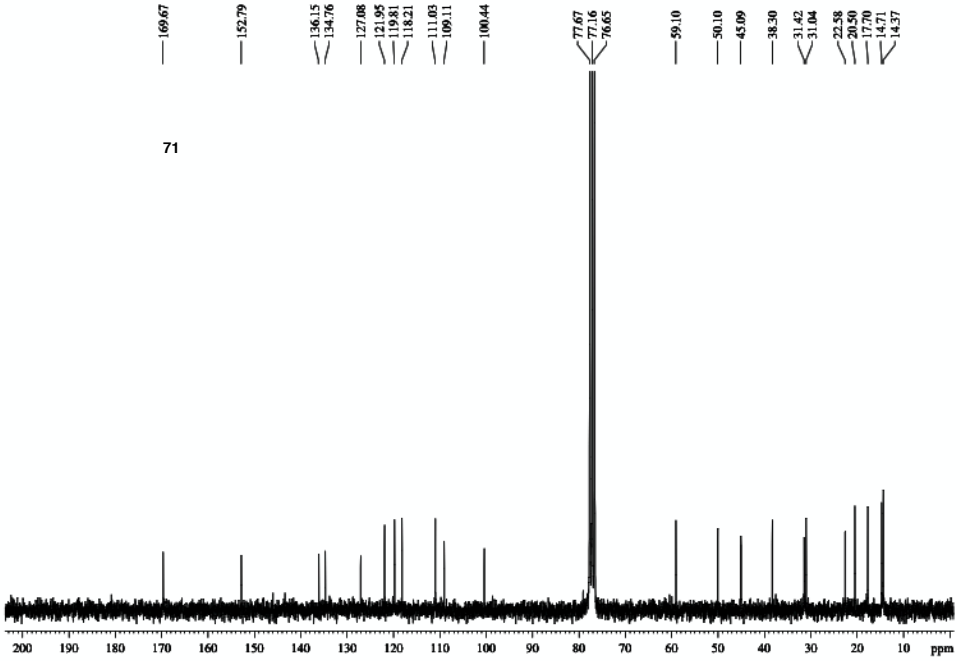

4.35
4.31
N
H
H
N
Me
O
Me
O
H
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

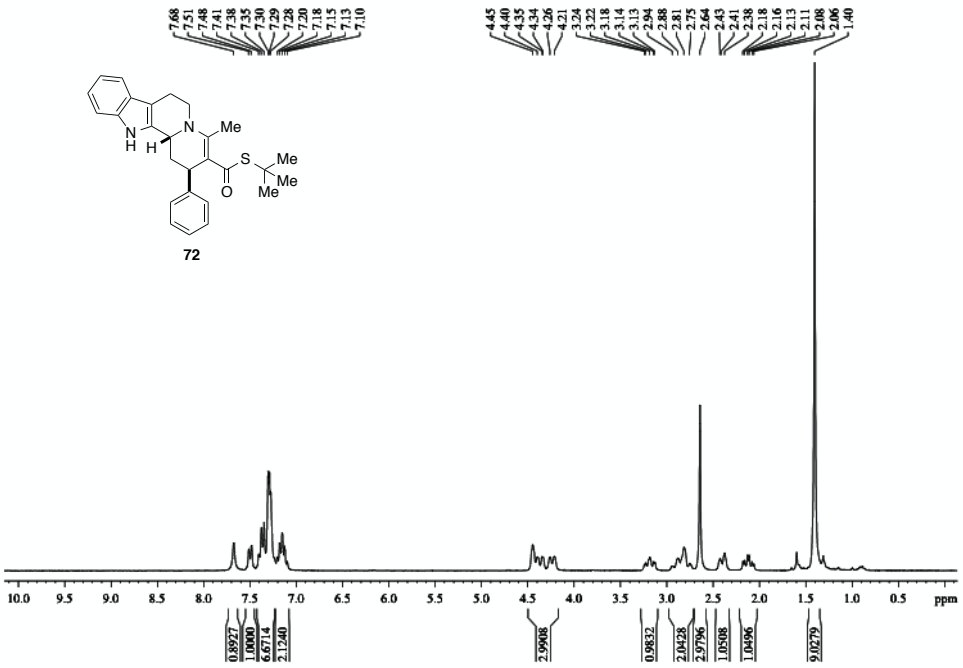
**69**

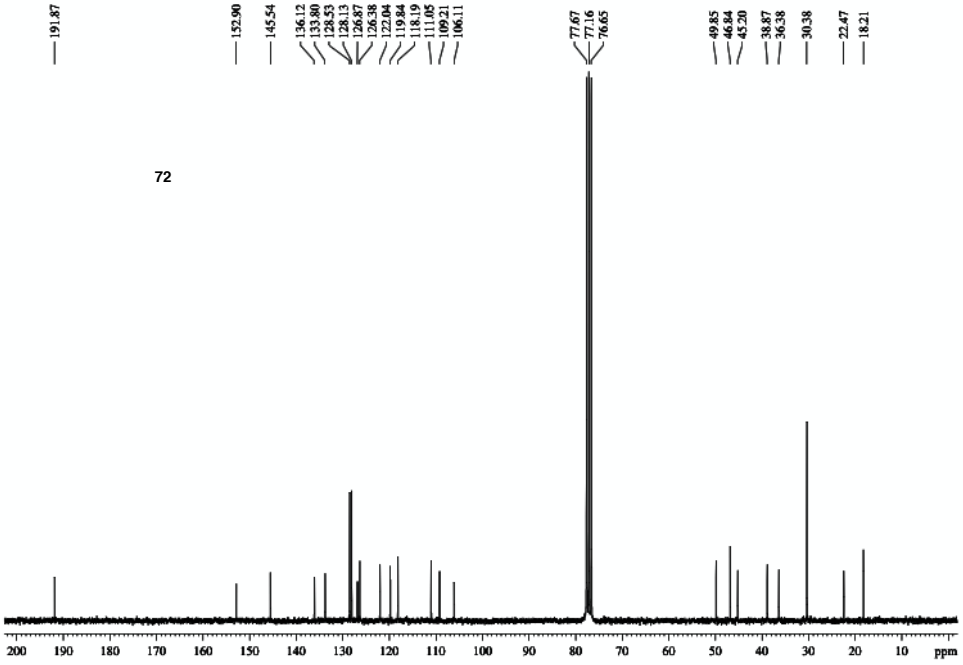

5.21
5.19
N
H
H
N
Me
O
Me
O
H
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

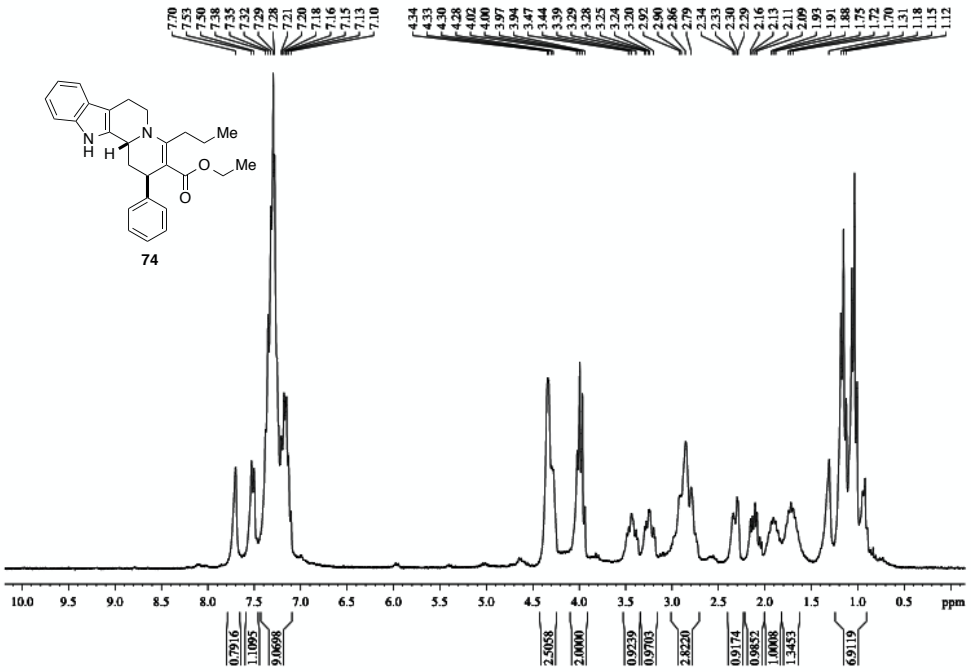
**69**

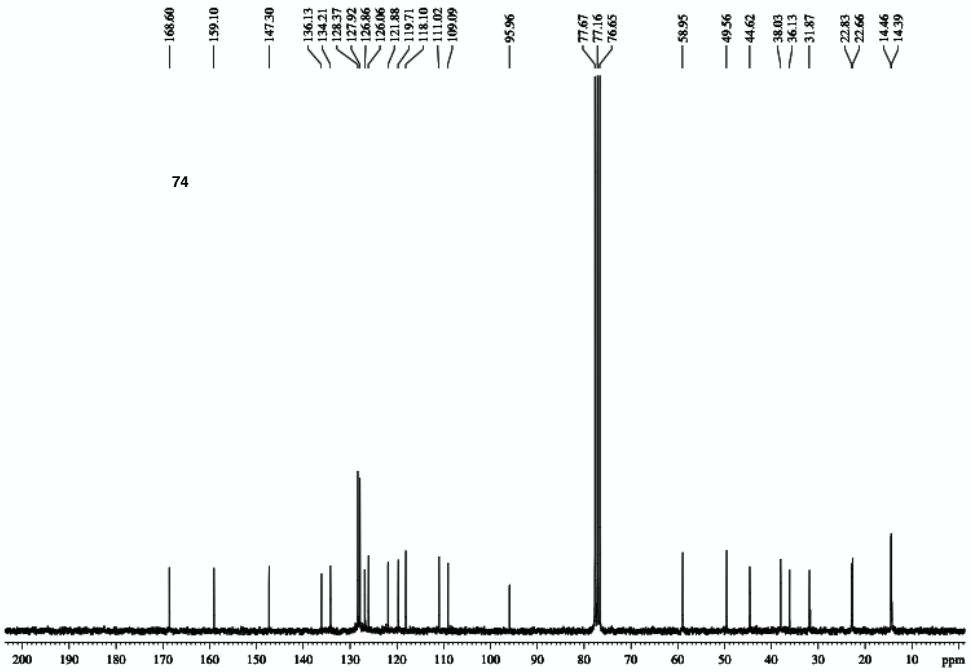

7.92 7.54 7.51 7.39 7.38 7.36 7.29 7.24 7.23 7.21 7.20 7.18 7.17 7.15 7.14 7.12 4.58 4.53 4.31 4.31 4.25 4.22 4.21 4.18 4.16 4.15 4.13 4.12 4.10 4.09 3.25 3.24 3.21 3.19 3.16 3.14 2.99 2.88 2.88 2.82 2.81 2.76 2.51 2.29 2.25 1.79 1.77 1.74 1.72 1.69 1.67 1.63 1.58 1.57 1.55 1.53 1.39
Me
N
H
N
H
Me
O
Me
O
Me
71
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.7909 0.8463 0.8240 0.5719 1.8151 0.8518 3.0000 0.8691 2.7140 2.6998 1.3556 9.7768 2.9734

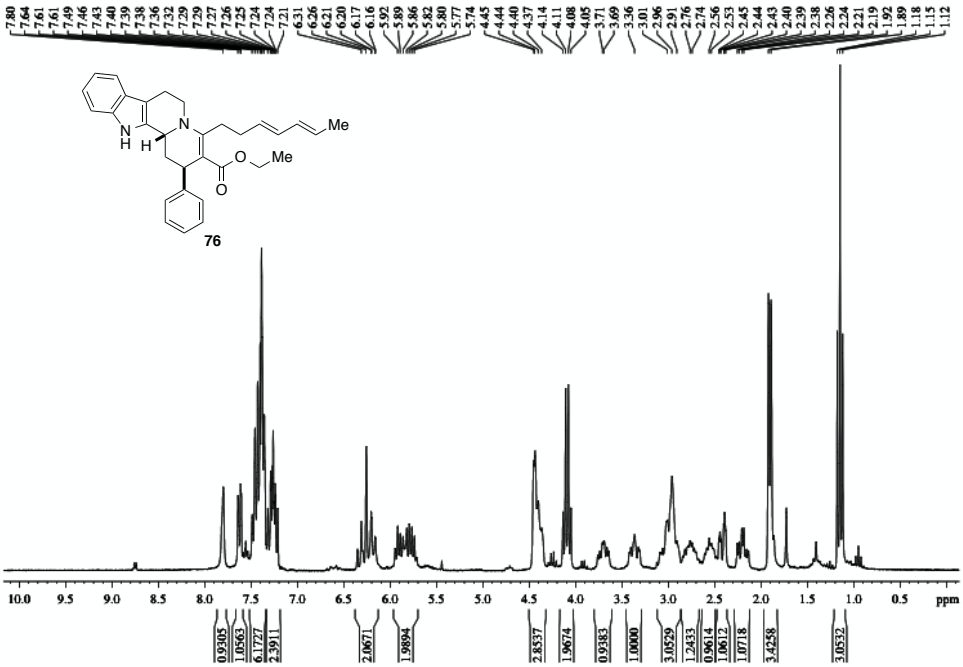

169.67 152.79 136.15 134.76 127.08 121.95 119.81 118.21 111.03 109.11 100.44 77.67 77.16 76.65 59.10 50.10 45.09 38.30 31.42 31.04 22.58 20.50 17.70 14.71 14.37
71
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

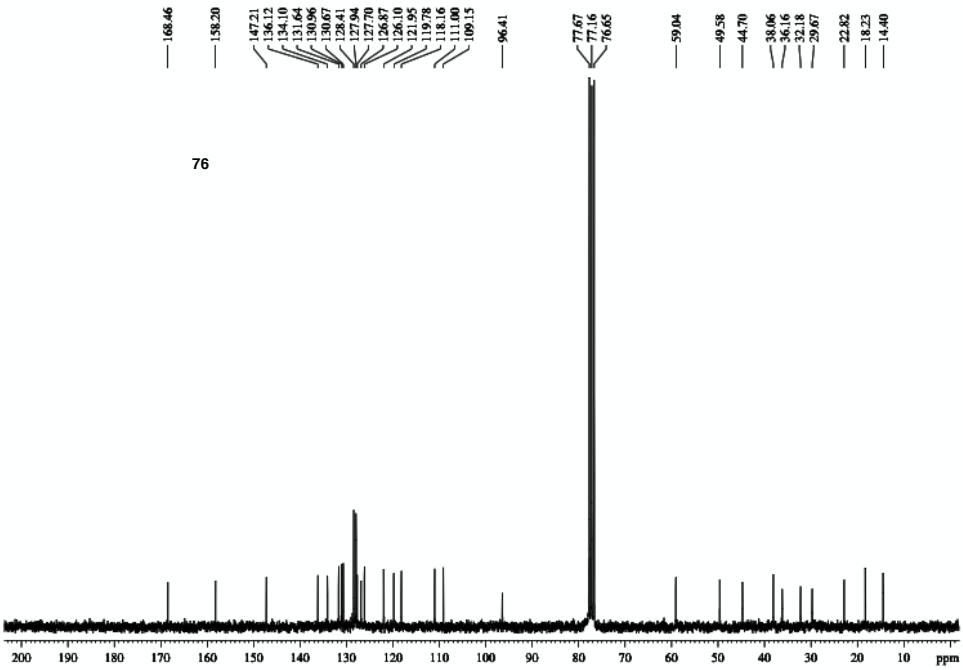

7.68
7.51
7.48
7.41
7.38
7.35
7.30
7.29
7.28
7.20
7.18
7.15
7.13
7.10
4.45
4.40
4.35
4.34
4.26
4.21
3.24
3.22
3.18
3.14
3.13
2.94
2.88
2.81
2.75
2.64
2.43
2.41
2.38
2.18
2.16
2.13
2.11
2.08
2.06
1.40
Me
N
H
N
H
S
Me
Me
Me
O
72
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8927
1.0000
6.6714
2.1240
2.9908
0.9832
2.0428
2.9796
1.0508
1.0496
9.1027

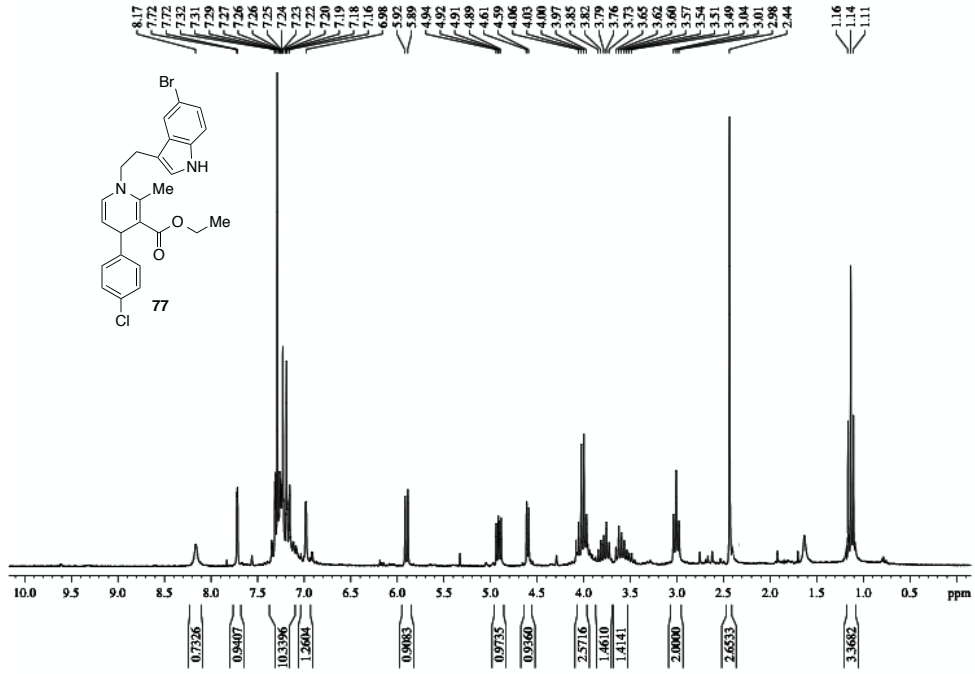

191.87
152.90
145.54
136.12
133.80
128.55
128.13
126.87
126.38
122.04
119.84
118.19
111.05
109.21
106.11
77.67
77.16
76.65
49.85
46.84
45.20
38.87
36.38
30.38
22.47
18.21
72
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.70
7.53
7.50
7.38
7.35
7.32
7.29
7.28
7.21
7.20
7.18
7.16
7.15
7.13
7.10
4.34
4.33
4.30
4.28
4.02
4.00
3.97
3.94
3.47
3.44
3.39
3.29
3.28
3.25
3.24
3.30
2.92
2.90
2.86
2.79
2.34
2.33
2.30
2.29
2.16
2.13
2.11
2.09
1.93
1.91
1.88
1.75
1.72
1.70
1.31
1.18
1.15
1.12
N
H
H
N
Me
O
Me
O
74
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.7916
1.1095
9.0698
2.5058
2.0000
0.9239
0.9703
2.8220
0.9174
0.9852
1.0008
1.3453
6.9119


168.60
159.10
147.30
136.13
134.21
128.37
127.92
126.86
126.06
121.88
119.71
118.10
111.02
109.09
95.96
77.67
77.16
76.65
58.95
49.56
44.62
38.03
36.13
31.87
22.83
22.66
14.46
14.39
74
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


7.80 7.64 7.61 7.61 7.49 7.46 7.43 7.40 7.39 7.38 7.36 7.32 7.29 7.29 7.27 7.26 7.25 7.24 7.24 7.21 6.31 6.26 6.21 6.20 6.17 6.16 5.92 5.89 5.86 5.82 5.80 5.77 5.74 4.45 4.44 4.40 4.37 4.14 4.11 4.08 4.05 3.71 3.69 3.56 3.01 2.96 2.91 2.76 2.74 2.56 2.53 2.45 2.44 2.43 2.40 2.39 2.38 2.26 2.24 2.21 2.19 1.92 1.89 1.18 1.15 1.12
Me
O
Me
O
76
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.9305 1.0563 6.1727 2.3911 2.0671 1.9894 2.8537 1.9674 0.9383 1.0000 3.0529 1.2433 0.9614 1.0612 1.0718 3.4258 3.0532


168.46 158.20 147.21 136.12 134.10 131.64 130.96 130.67 128.41 127.94 127.70 126.87 126.10 121.95 119.78 118.16 111.00 109.15 96.41 77.67 77.16 76.65 59.04 49.58 44.70 38.06 36.16 32.18 29.67 22.82 18.23 14.40
76
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.17 7.72 7.72 7.32 7.31 7.29 7.27 7.26 7.26 7.25 7.24 7.23 7.22 7.20 7.19 7.18 7.16 6.98 5.92 5.89 4.94 4.92 4.91 4.89 4.61 4.59 4.06 4.03 4.00 3.97 3.85 3.82 3.79 3.76 3.73 3.65 3.62 3.60 3.57 3.54 3.51 3.49 3.04 3.01 2.98 2.44 1.16 1.14 1.11
Br
NH
N
Me
O
Me
O
77
Cl
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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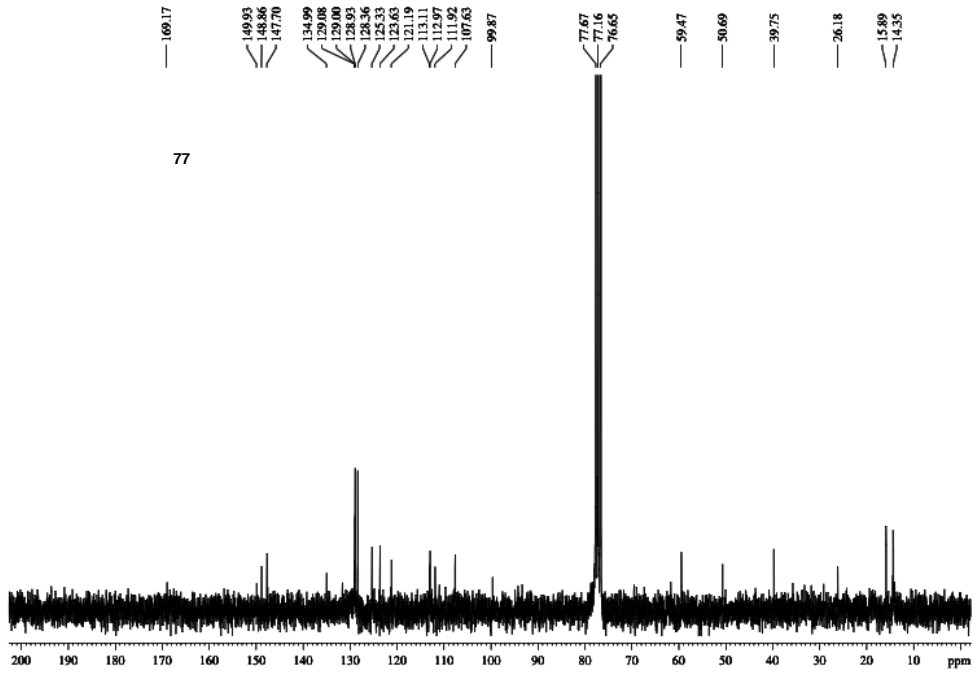
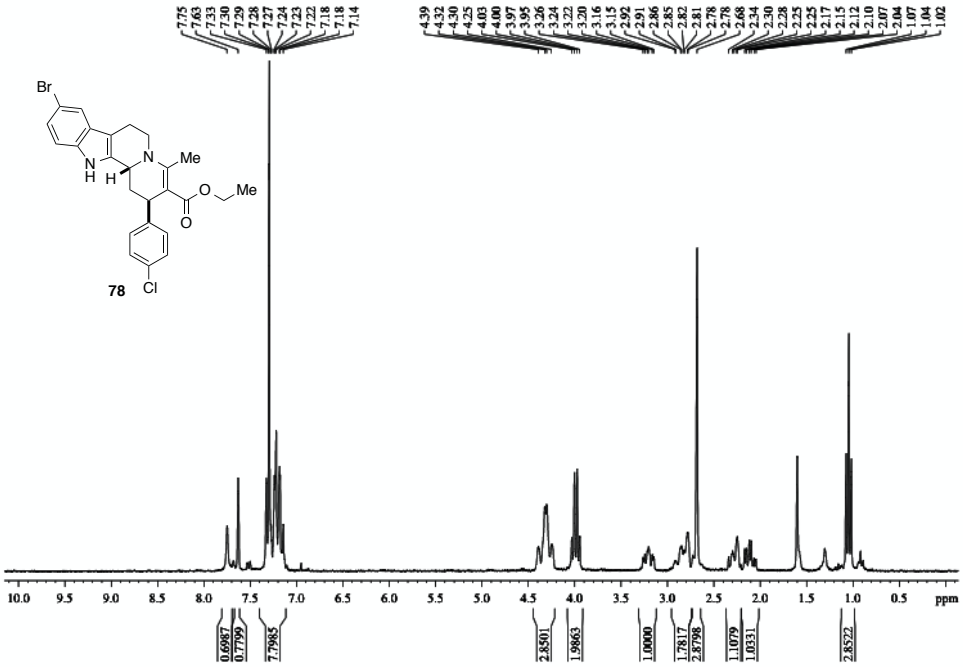

169.17
149.93 148.86 147.70 134.99 129.08 129.00 128.93 128.36 125.33 123.63 121.19 113.11 112.97 111.92 107.63 99.87 77.67 77.16 76.65 59.47 50.69 39.75 26.18 15.89 14.35
77
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.75
7.63
7.33
7.30
7.29
7.28
7.27
7.24
7.23
7.22
7.18
7.14
4.39
4.32
4.30
4.25
4.03
4.00
3.97
3.95
3.26
3.24
3.22
3.20
3.16
3.15
2.92
2.91
2.86
2.85
2.82
2.81
2.78
2.78
2.68
2.34
2.30
2.28
2.25
2.25
2.17
2.15
2.12
2.10
2.07
2.04
1.07
1.04
1.02
Br
N
H
N
H
Me
O
Me
O
Cl
78
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.6987
0.7799
7.7985
2.8501
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1.7817
2.8798
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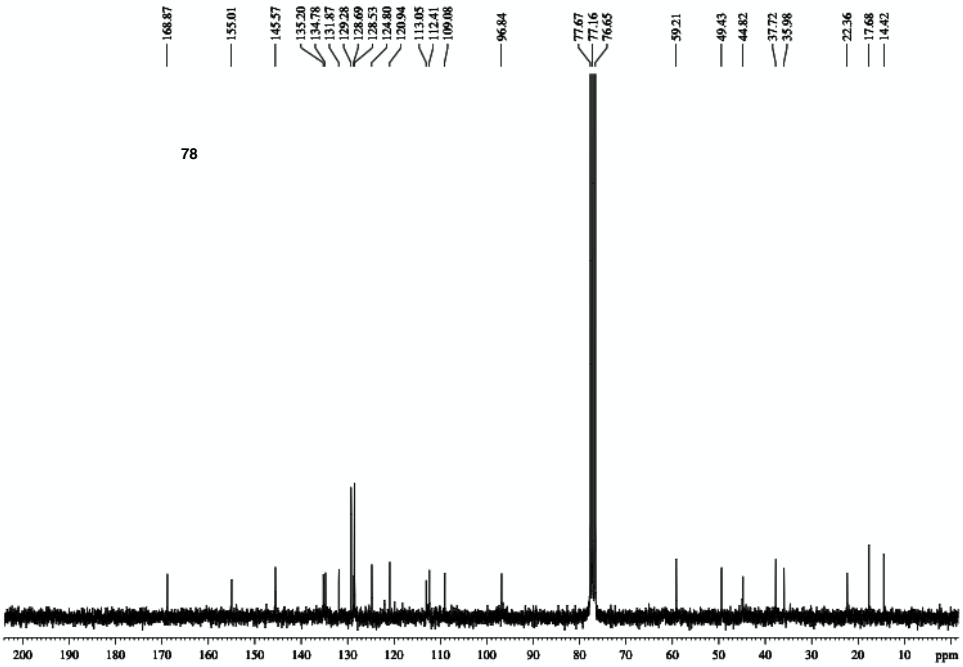
1.0331
2.8522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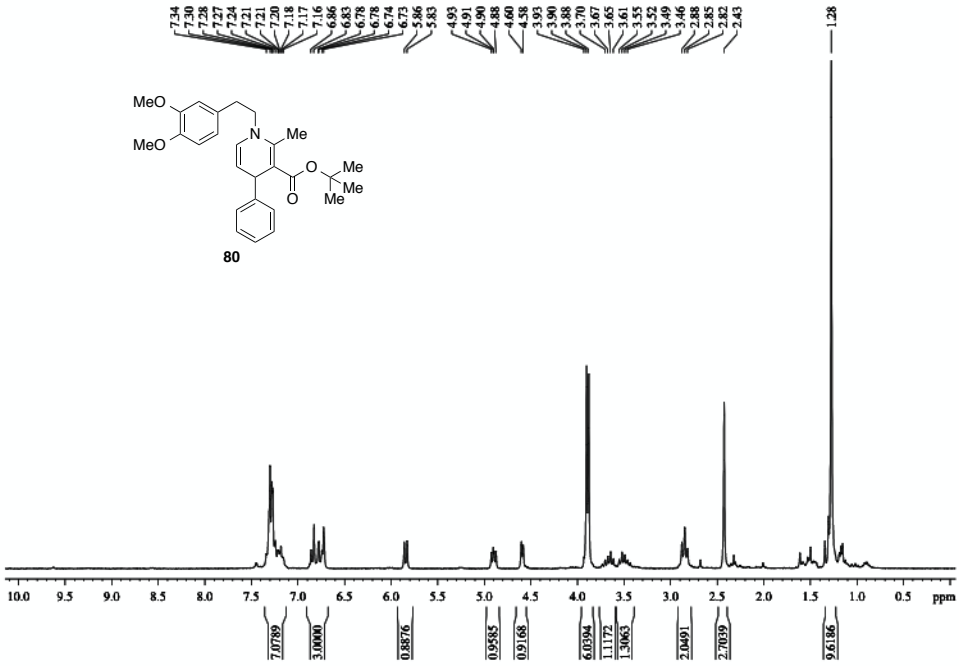
134.78
131.87
129.28
128.69
128.53
124.80
120.94
113.05
112.41
109.08
96.84
77.67
77.16
76.65
59.21
49.43
44.82
37.72
35.98
22.36
17.68
14.42
78
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.28
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7.20
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7.16
6.86
6.83
6.78
6.78
6.74
6.73
5.86
5.83
4.93
4.91
4.90
4.88
4.60
4.58
3.93
3.90
3.88
3.70
3.67
3.65
3.61
3.55
3.52
3.49
3.46
2.88
2.85
2.82
2.43
1.28
MeO
MeO
N
Me
O
Me
Me
Me
O
80
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
7.0789
3.0000
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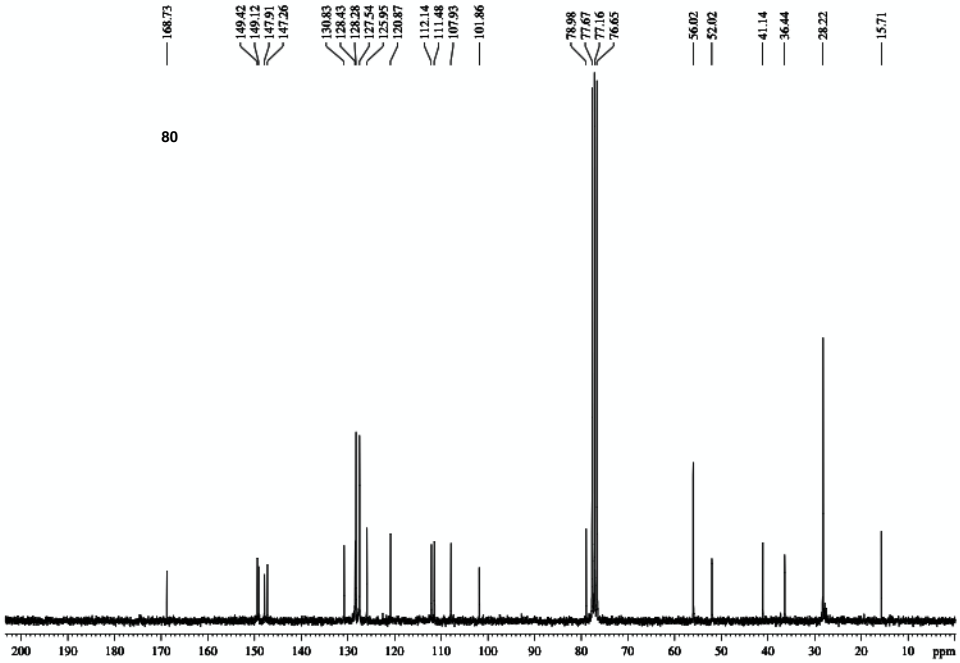
0.9585
0.9168
6.0394
1.1172
1.3063
2.0491
2.7039
9.6186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125.95
120.87
112.14
111.48
107.93
101.86
78.98
77.67
77.16
76.65
56.02
52.02
41.14
36.44
28.22
15.71
80
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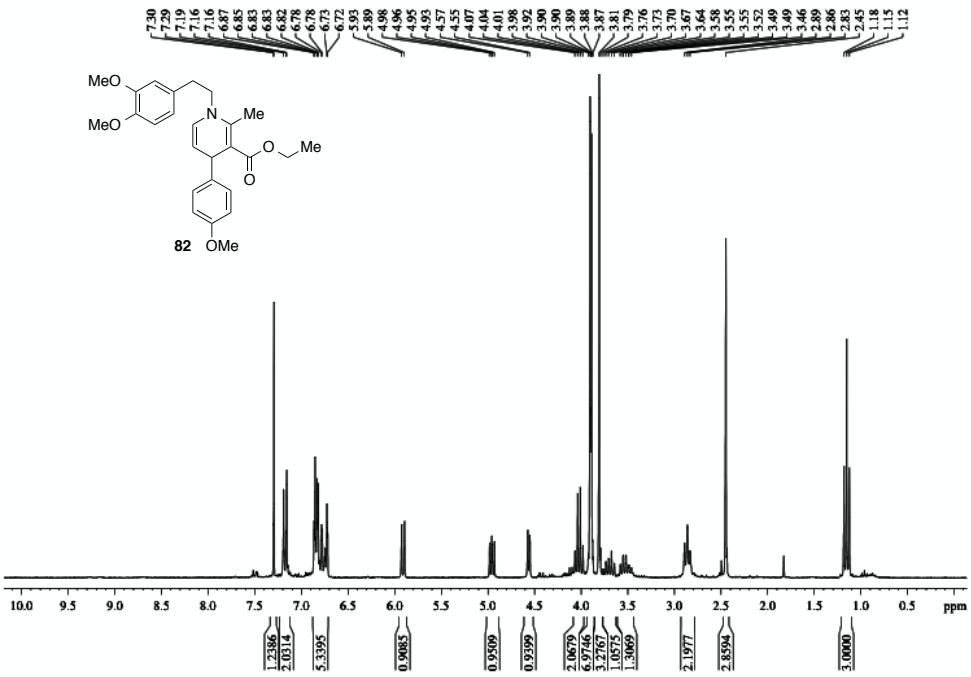
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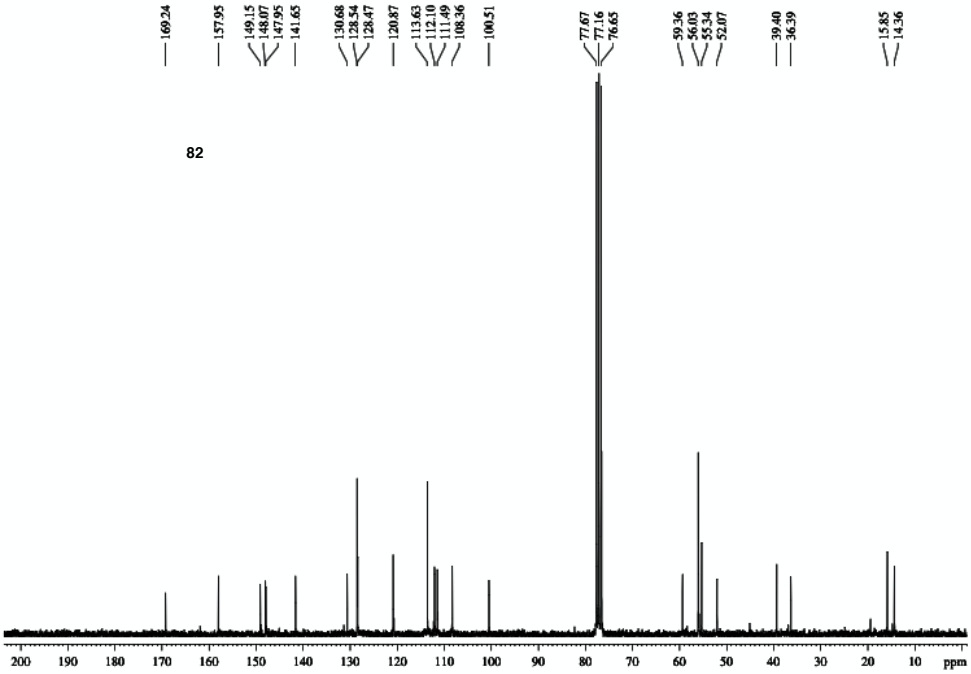
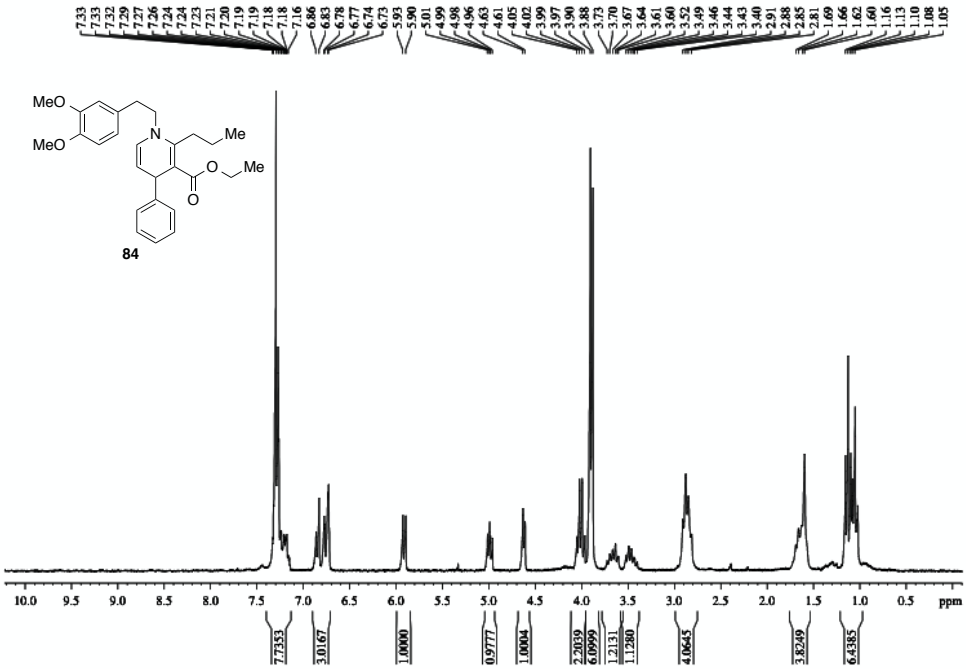
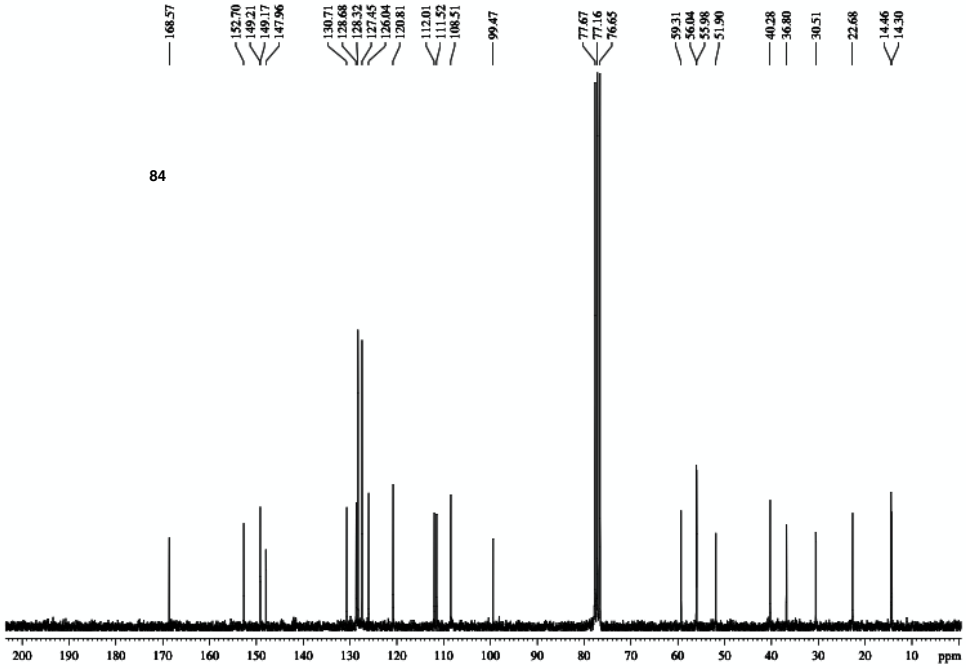
MeO
N
Me
O
Me
O
82
OMe
ppm


82
ppm


MeO
MeO
N
Me
O
Me
O
84
ppm


84
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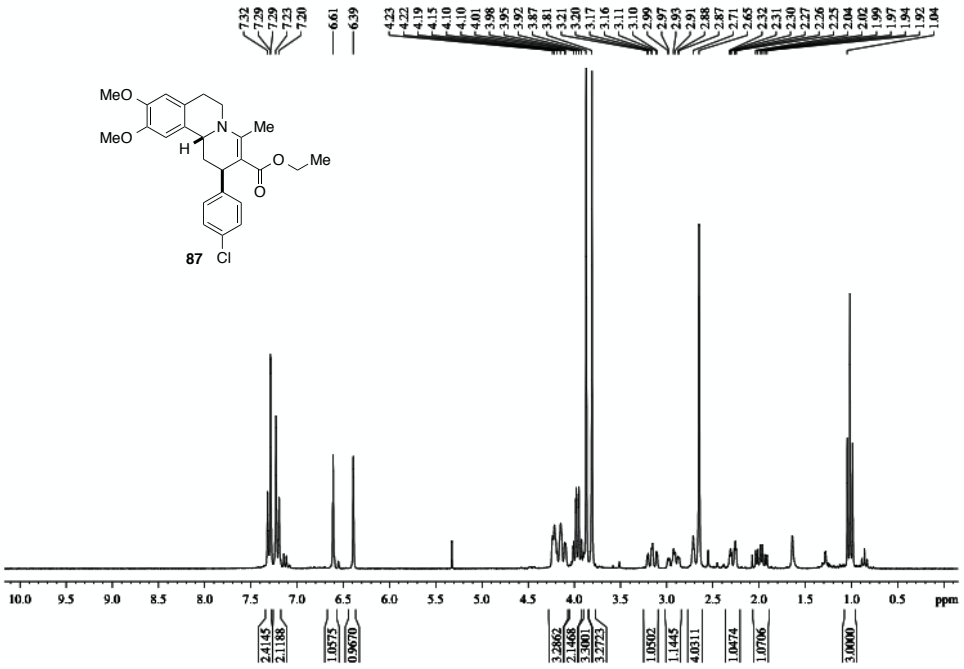
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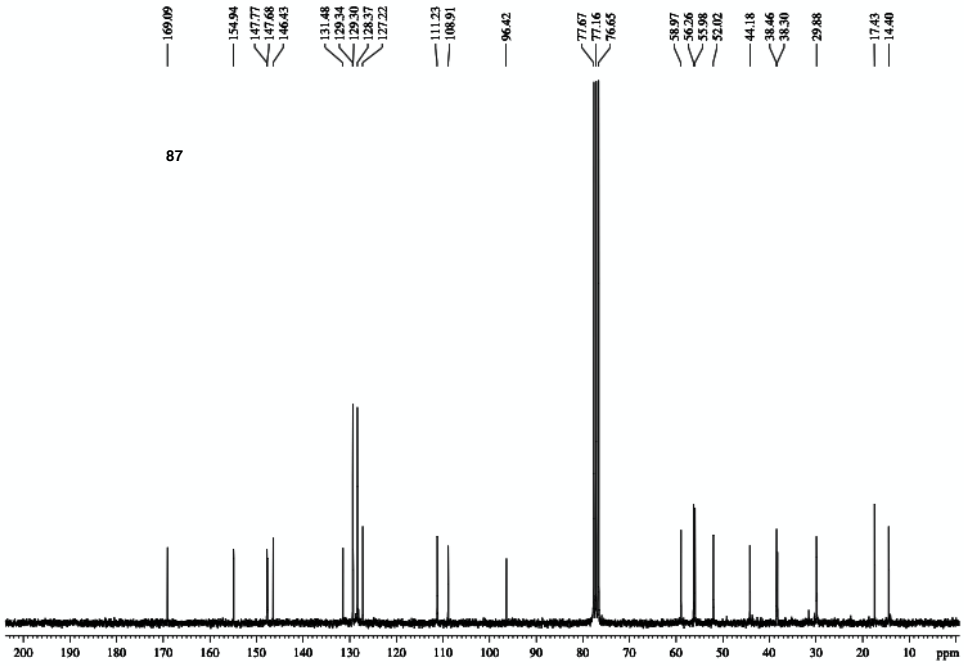
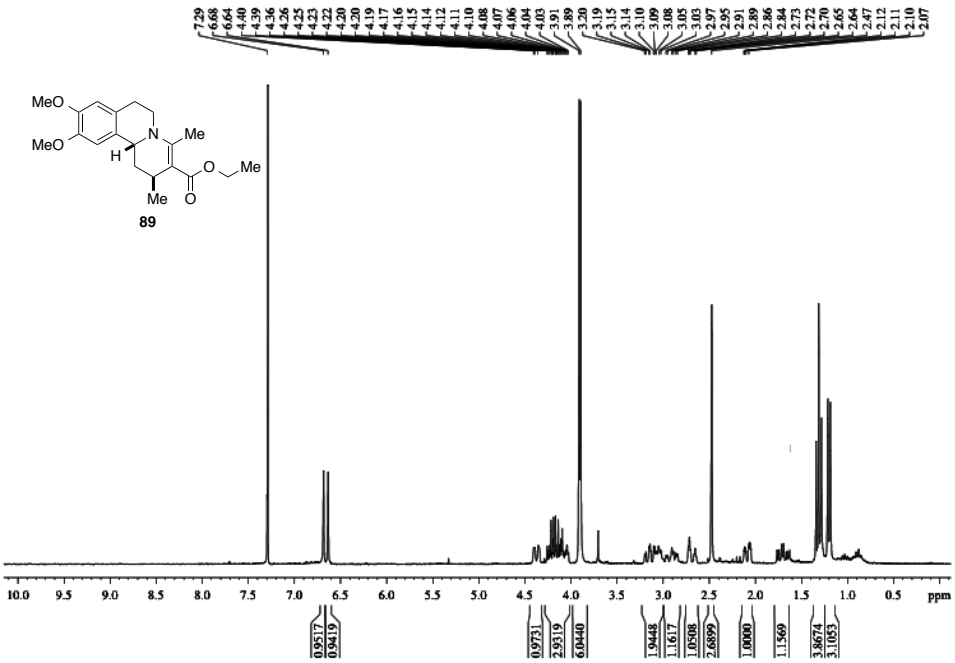
MeO
N
H
Me
O
O
Me
Cl
87
ppm


87
ppm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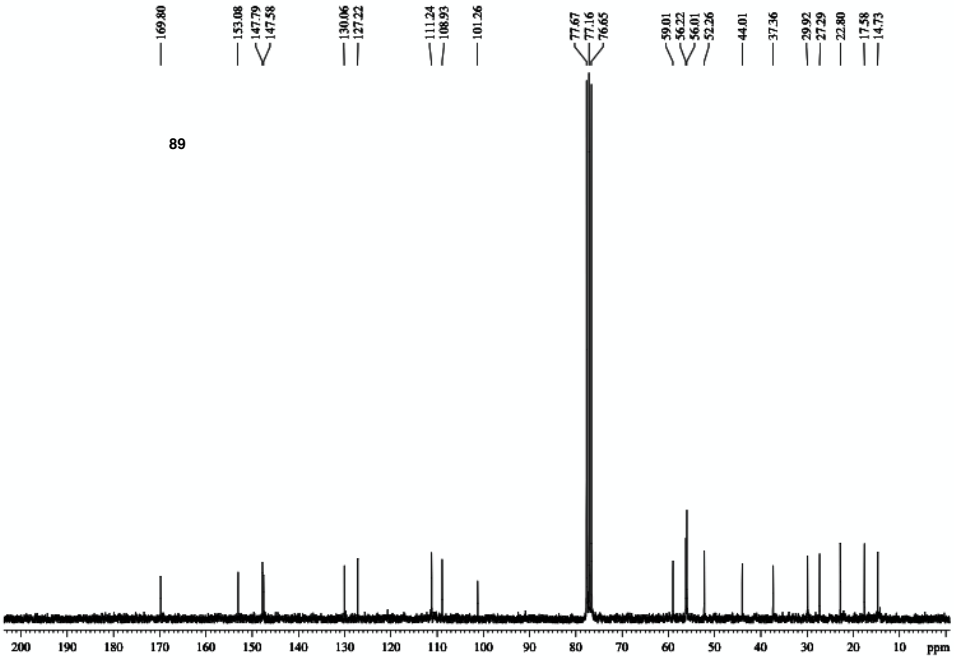
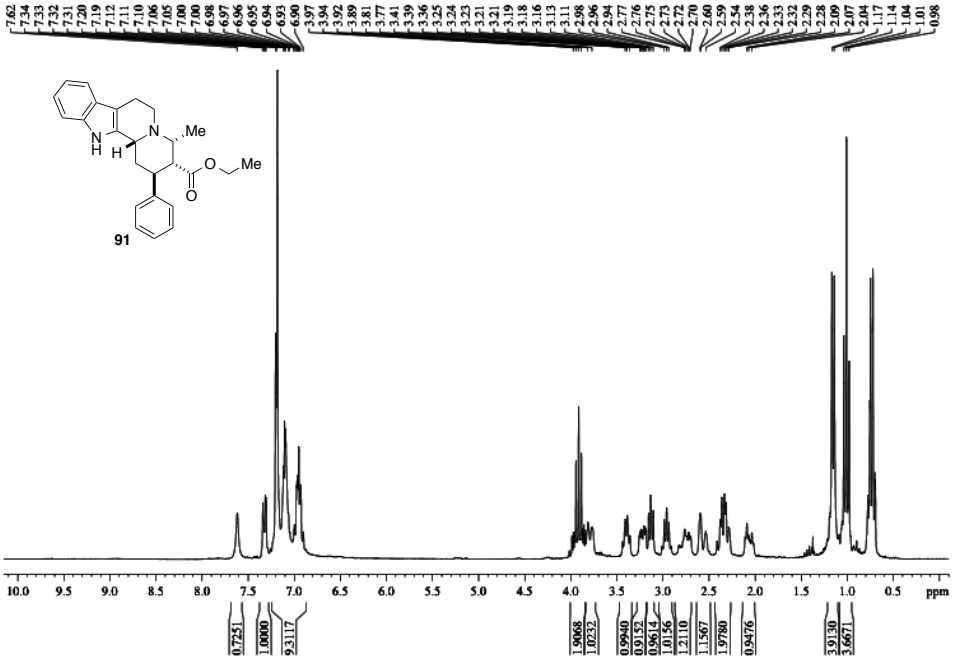
MeO
H
N
Me
O
Me
Me
O
89
ppm


89
ppm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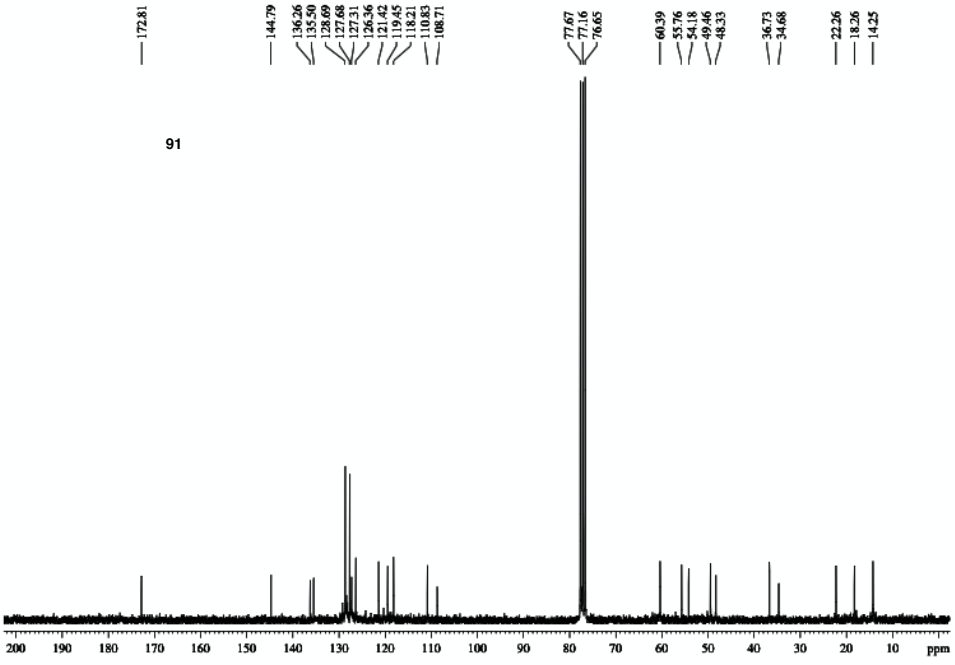
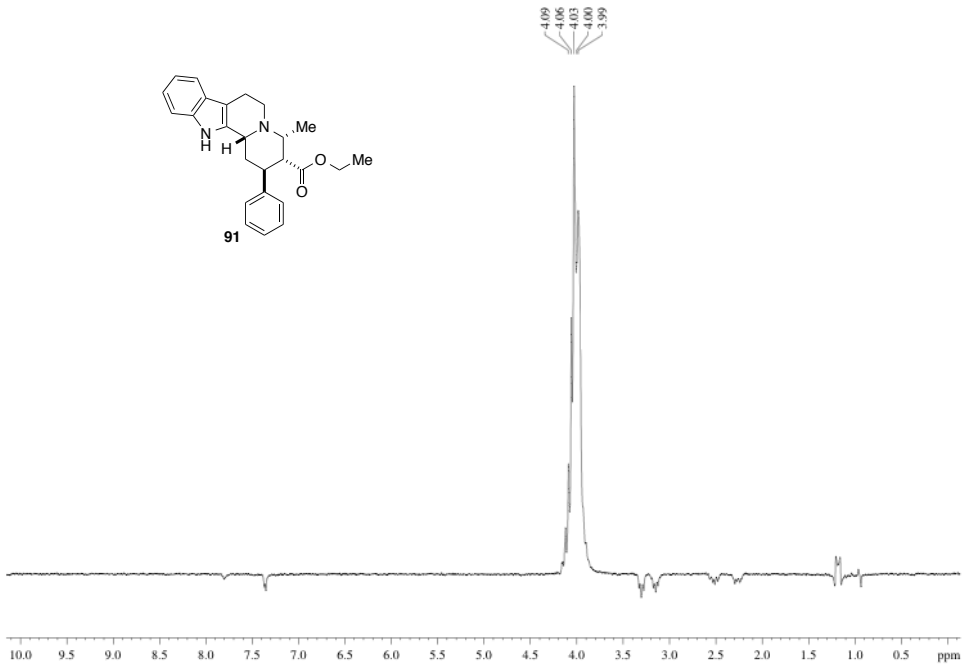
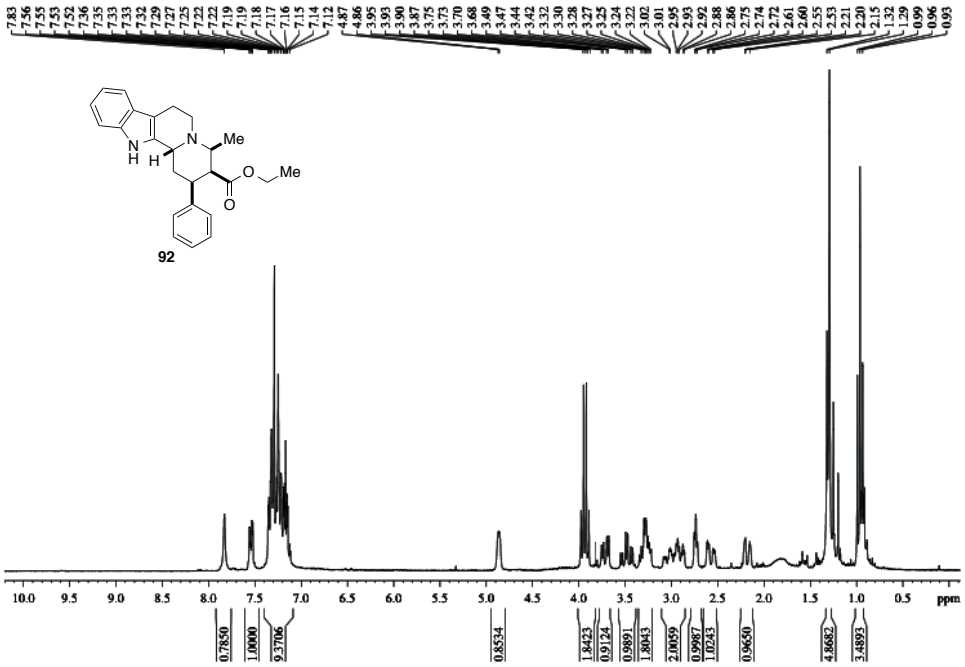
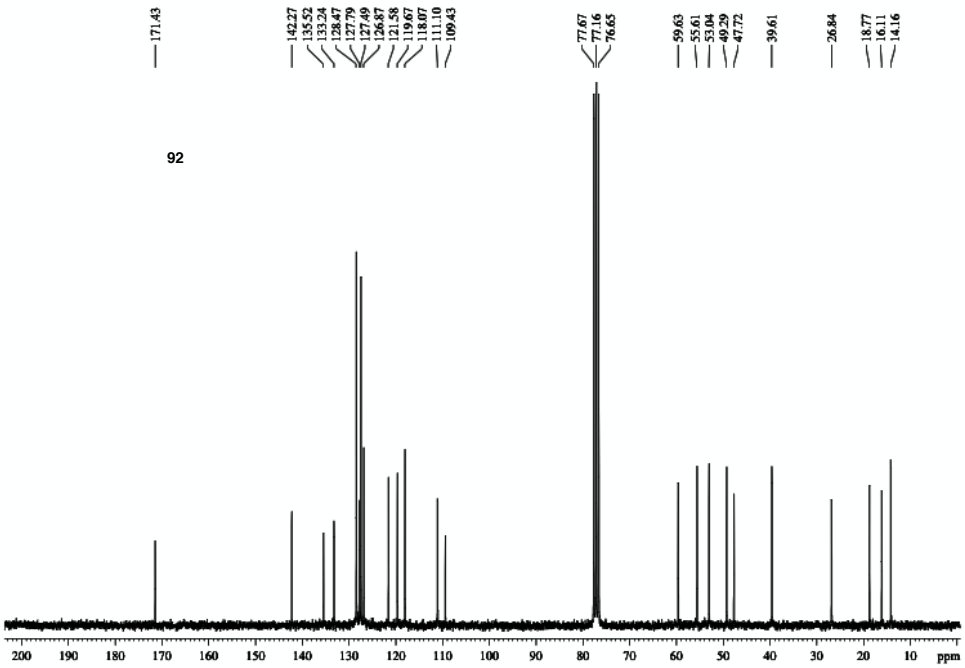
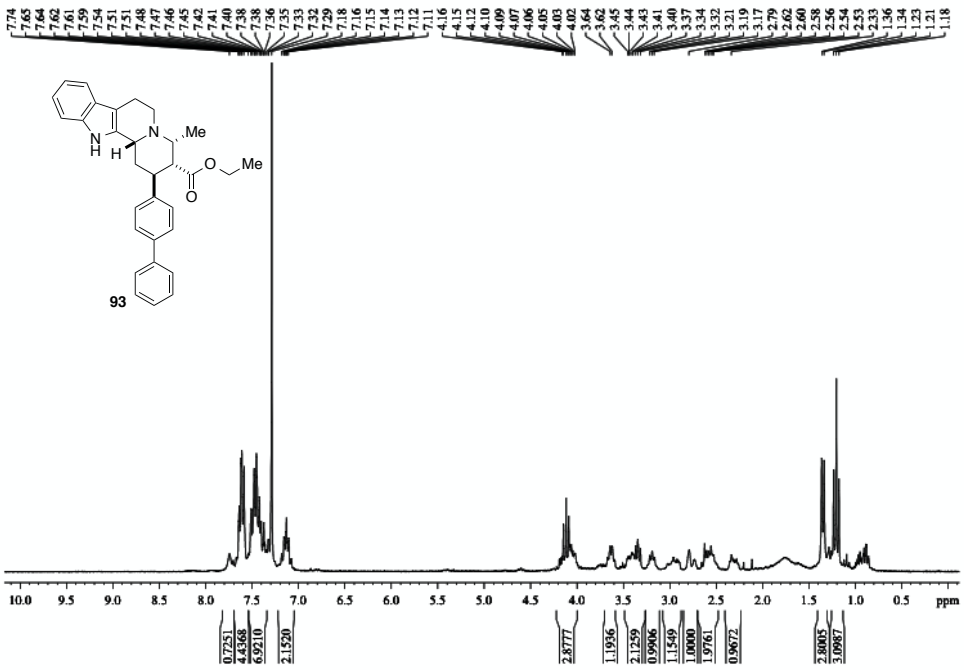
N
H
N
Me
O
O
Me
91
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.7251 1.0000 2.3117 1.9068 1.0232 0.9940 0.9152 0.9614 1.0156 1.2110 1.1567 1.9780 0.9476 3.9130 3.6671

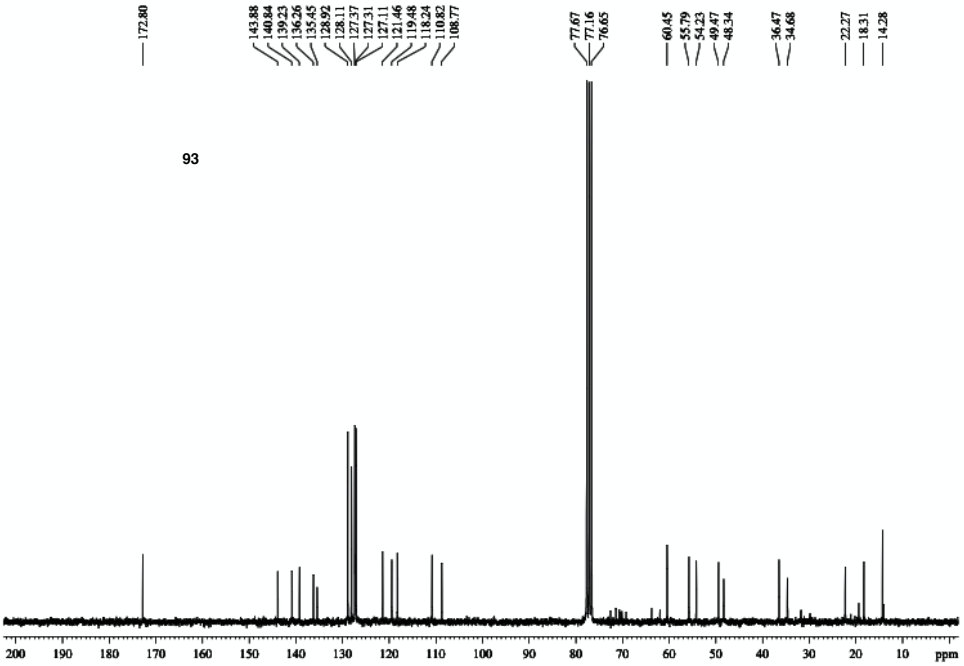

172.81 144.79 136.26 135.50 128.69 127.68 127.31 126.36 121.42 119.45 118.21 110.83 108.71 77.67 77.16 76.65 60.39 55.76 54.18 49.46 48.33 36.73 34.68 22.26 18.26 14.25
91
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

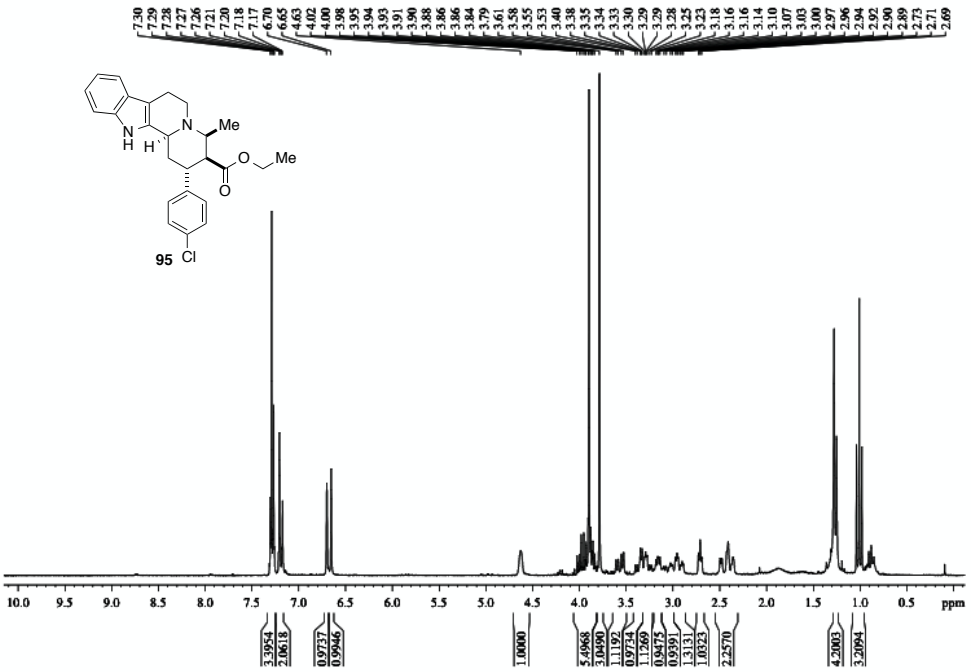

4.09
4.06
4.03
4.00
3.99
N
H
N
H
Me
O
Me
O
91
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


7.83 7.56 7.55 7.53 7.52 7.36 7.35 7.33 7.32 7.29 7.27 7.25 7.22 7.22 7.19 7.19 7.18 7.17 7.16 7.15 7.14 7.12 4.87 4.86 3.95 3.93 3.90 3.87 3.75 3.73 3.70 3.68 3.49 3.47 3.44 3.42 3.32 3.30 3.28 3.27 3.25 3.24 3.22 3.02 3.01 2.95 2.93 2.92 2.88 2.86 2.75 2.74 2.72 2.61 2.60 2.55 2.53 2.21 2.20 2.15 1.32 1.29 0.99 0.96 0.93
N H
N
Me
O
Me
O
92
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.7850 1.0000 9.3706 0.8534 1.8423 0.9124 0.9891 1.8043 2.0859 0.9987 1.0243 0.9650 4.8682 3.4893


171.43
142.27 135.52 133.24 128.47 127.79 127.49 126.87 121.58 119.67 118.07 111.10 109.43
77.67 77.16 76.65
59.63 55.61 53.04 49.29 47.72
39.61
26.84
18.77 16.11 14.16
92
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


93
Me
Me
O
O
N
H
ppm


93
ppm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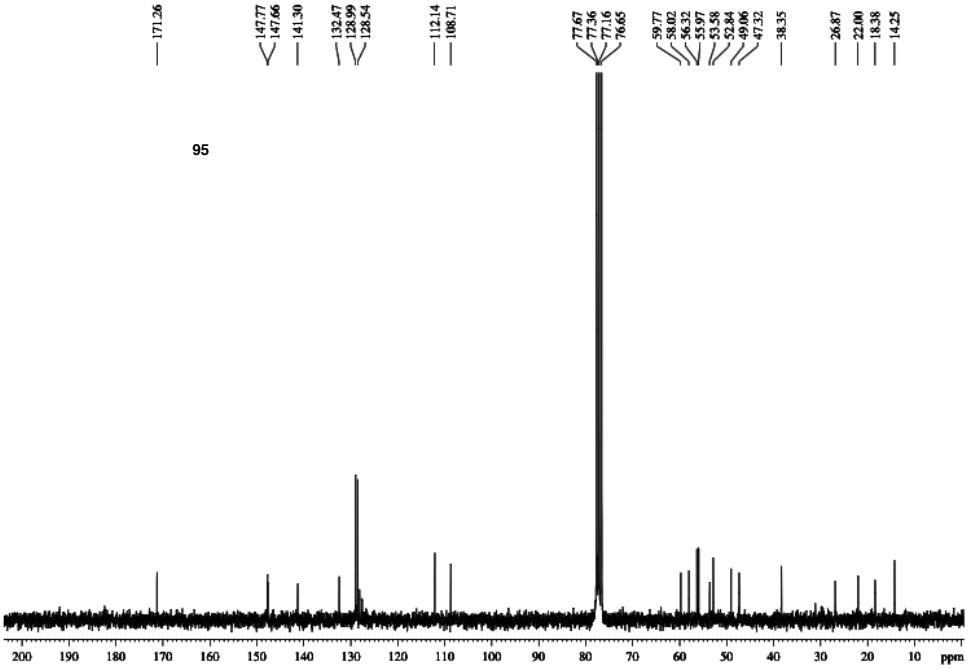
N
H
H
N
Me
O
O
Me
95
Cl
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.3954
2.0618
0.9737
0.9946
1.0000
5.4968
3.0490
1.1197
0.9734
1.1260
0.9475
0.9391
1.3131
1.0323
2.2570
4.2003
3.2094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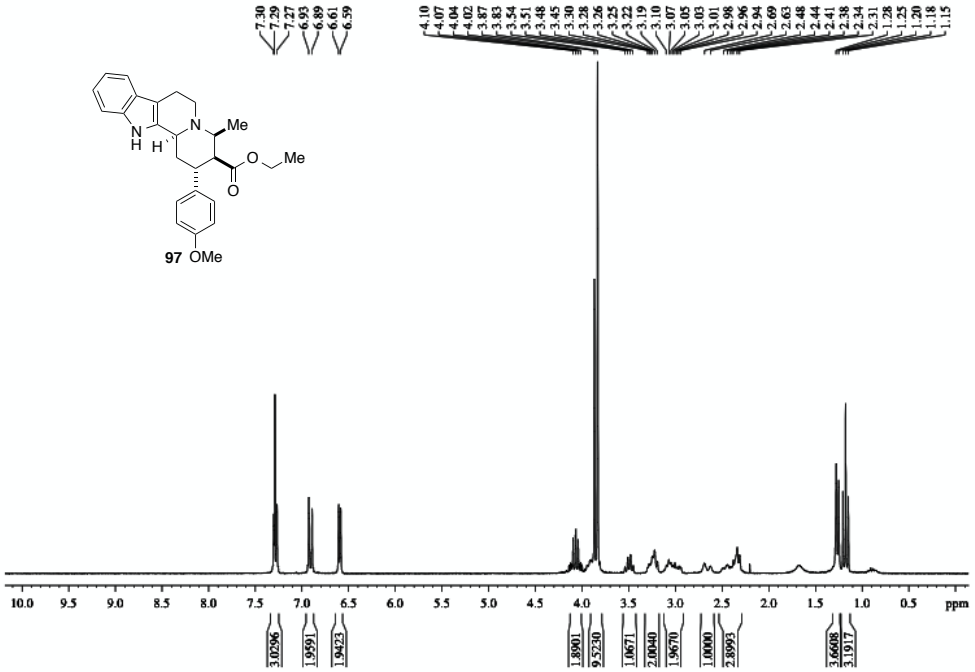
128.54
112.14
108.71
77.67
77.36
77.16
76.65
59.77
58.02
56.32
55.97
53.58
52.84
49.06
47.32
38.35
26.87
22.00
18.38
14.25
95
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.27
6.93
6.89
6.61
6.59
4.10
4.07
4.04
4.02
3.87
3.83
3.54
3.51
3.48
3.45
3.30
3.28
3.26
3.25
3.22
3.19
3.10
3.07
3.05
3.03
3.01
2.98
2.96
2.94
2.69
2.63
2.48
2.44
2.41
2.38
2.34
2.31
1.28
1.25
1.20
1.18
1.15
N
H
H
N
Me
O
Me
O
97 OMe
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.0296
1.9591
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3.8901
9.5230
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2.0040
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1.0000
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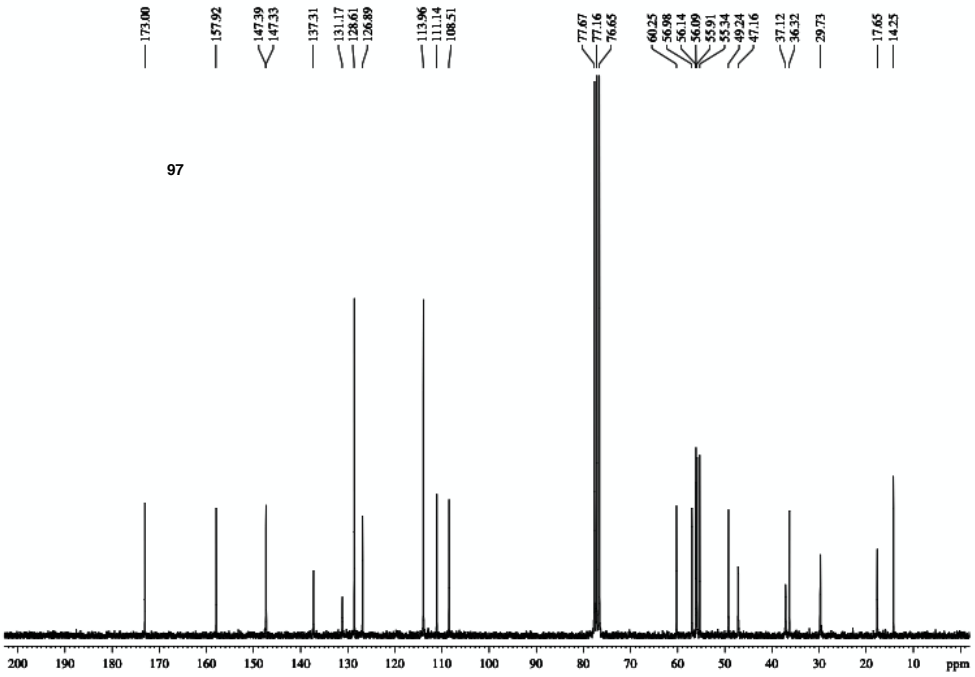
3.6608
3.1917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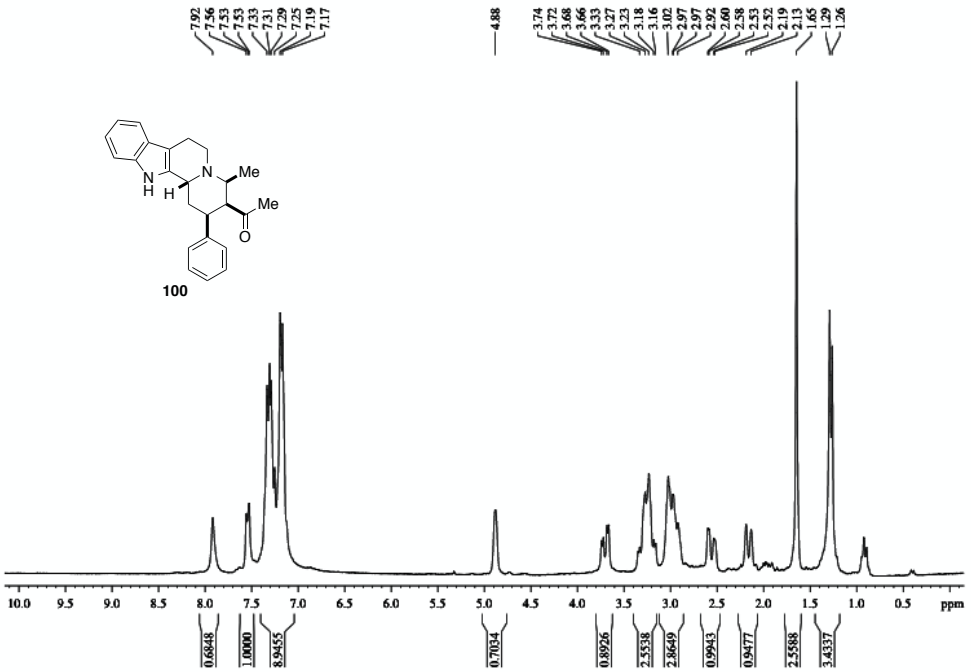
157.92
147.39
147.33
137.31
131.17
128.61
126.89
113.96
111.14
108.51
77.67
77.16
76.65
60.25
56.98
56.14
56.09
55.91
55.34
49.24
47.16
37.12
36.32
29.73
17.65
14.25
97
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.31
7.29
7.25
7.19
7.17
4.88
3.74
3.72
3.68
3.66
3.33
3.27
3.23
3.18
3.16
3.02
2.97
2.97
2.92
2.60
2.58
2.53
2.52
2.19
2.13
1.65
1.29
1.26
N
H
N
H
Me
Me
O
100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.6648
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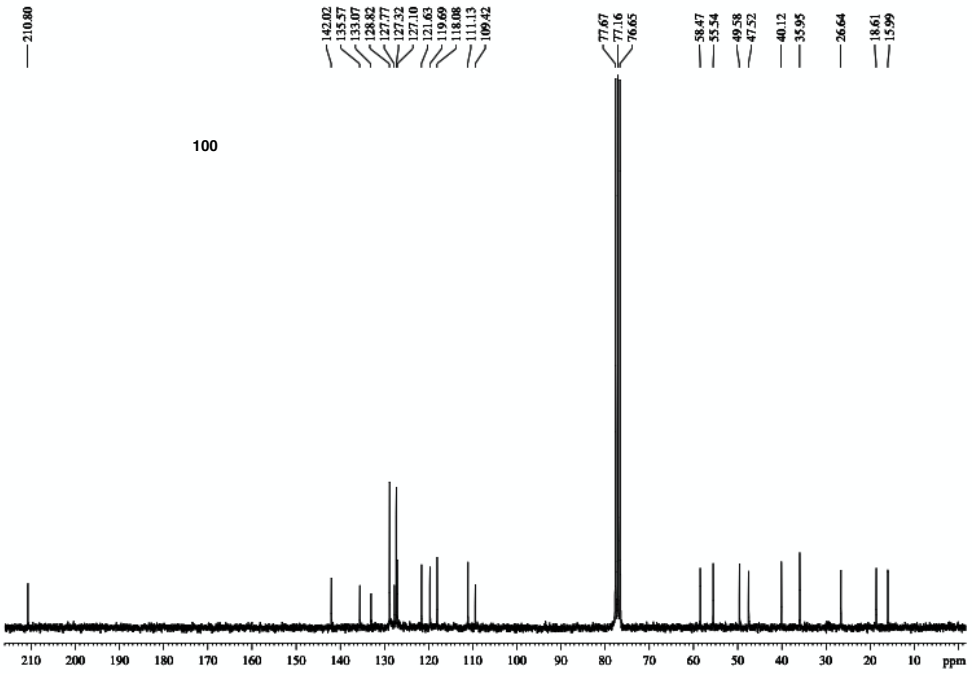
0.7034
0.8926
2.5538
2.8649
0.9943
0.9477
2.5588
3.4337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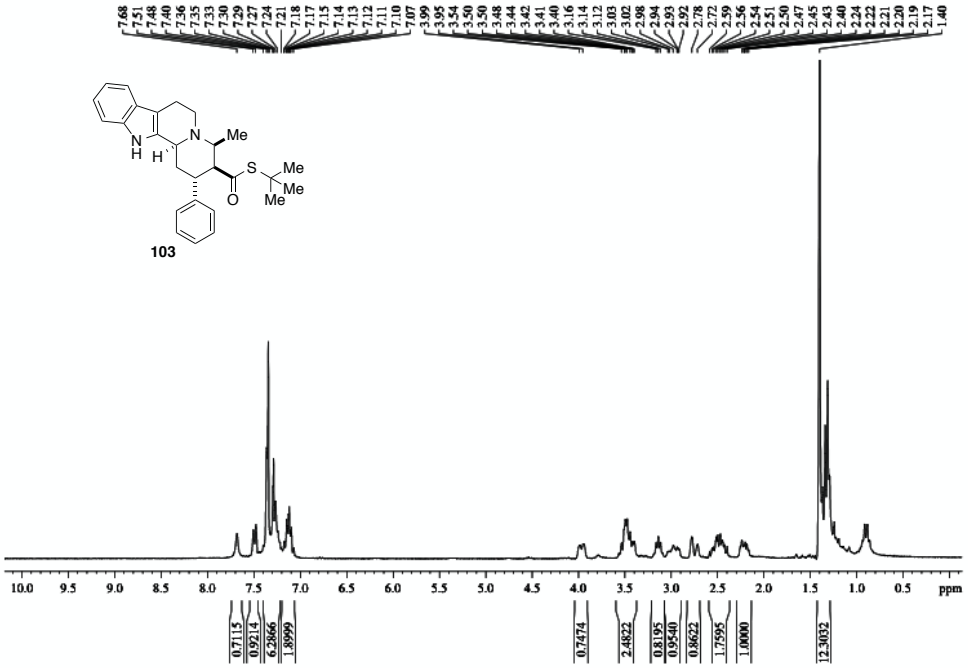
133.07
128.82
127.77
127.32
127.10
121.63
119.69
118.08
111.13
109.42
77.67
77.16
76.65
58.47
55.54
49.58
47.52
40.12
35.95
26.64
18.61
15.99
100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.30
7.29
7.27
7.24
7.21
7.18
7.17
7.15
7.14
7.13
7.12
7.11
7.10
7.07
3.99
3.95
3.54
3.50
3.50
3.48
3.44
3.42
3.41
3.40
3.16
3.14
3.12
3.03
3.02
2.98
2.94
2.93
2.92
2.78
2.72
2.59
2.56
2.54
2.51
2.50
2.47
2.45
2.43
2.40
2.24
2.22
2.21
2.20
2.19
2.17
1.40
Me
N
H
N
H
S
Me
Me
Me
O
103
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.7115
0.9214
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0.8622
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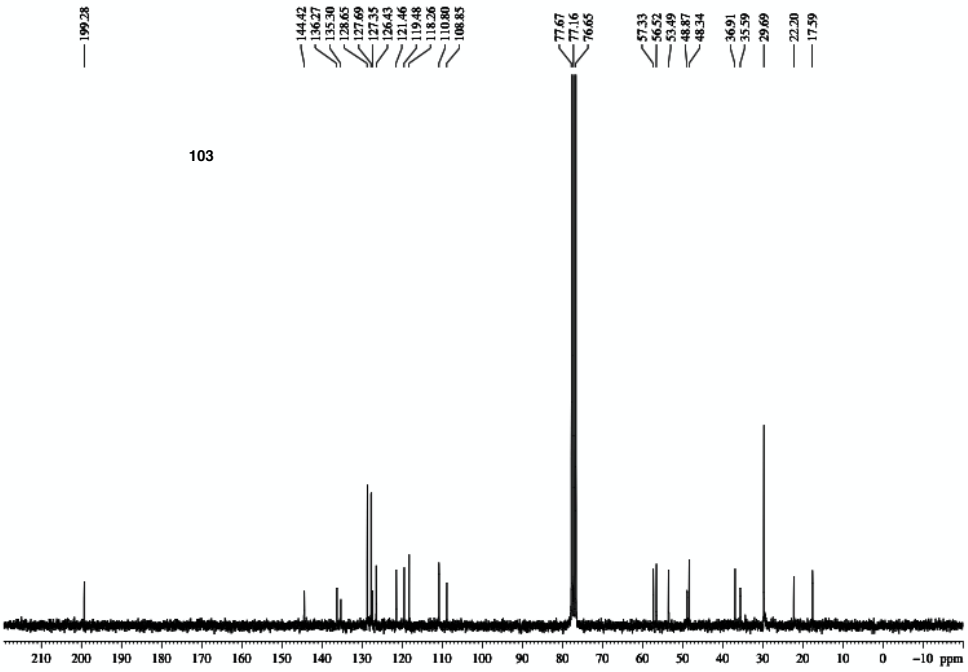
1.0000
12.3032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135.30
128.65
127.69
127.35
126.43
121.46
119.48
118.26
110.80
108.85
77.67
77.16
76.65
57.33
56.52
53.49
48.87
48.34
36.91
35.59
29.69
22.20
17.59
103
210
200
190
180
170
160
150
140
130
120
110
100
90
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50
40
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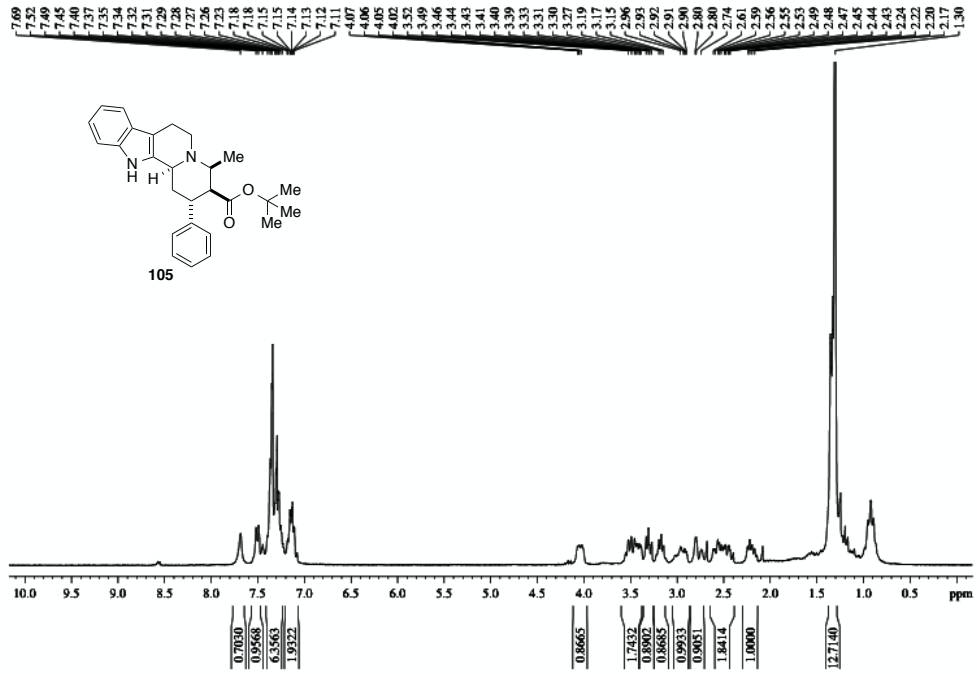
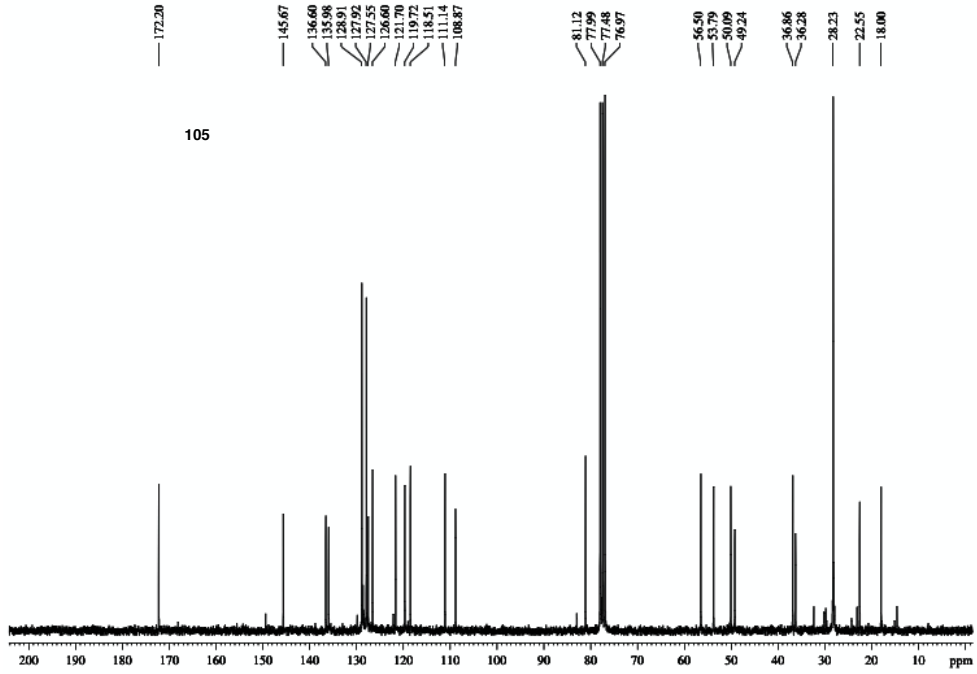
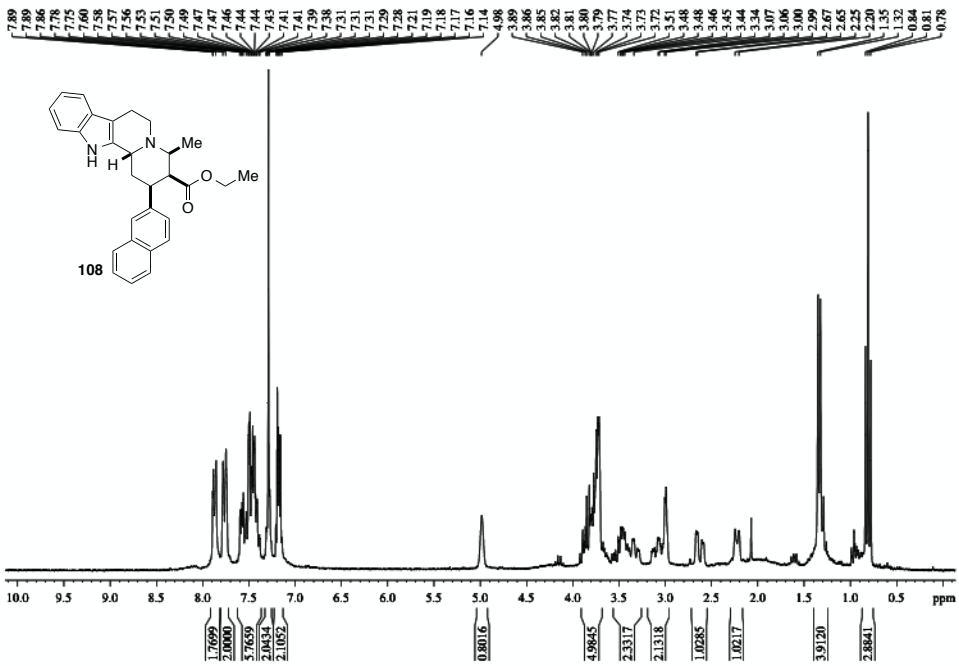
20
10
0
−10
ppm


105
ppm


105
ppm


7.89 7.89 7.86 7.78 7.75 7.60 7.58 7.57 7.56 7.53 7.51 7.50 7.49 7.47 7.47 7.46 7.44 7.44 7.43 7.41 7.41 7.39 7.38 7.31 7.31 7.31 7.29 7.28 7.21 7.19 7.18 7.17 7.16 7.14 4.98 3.89 3.86 3.85 3.82 3.81 3.80 3.79 3.77 3.74 3.73 3.72 3.51 3.48 3.48 3.46 3.45 3.44 3.34 3.07 3.06 3.00 2.99 2.67 2.65 2.25 2.20 1.35 1.32 0.84 0.81 0.78
N
H
N
Me
O
Me
O
108
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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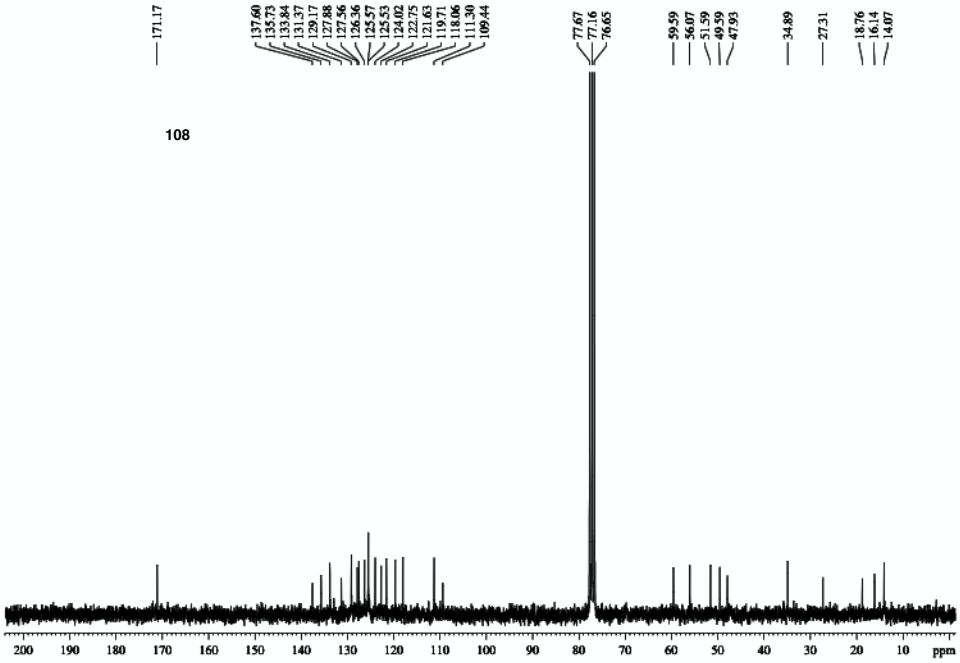
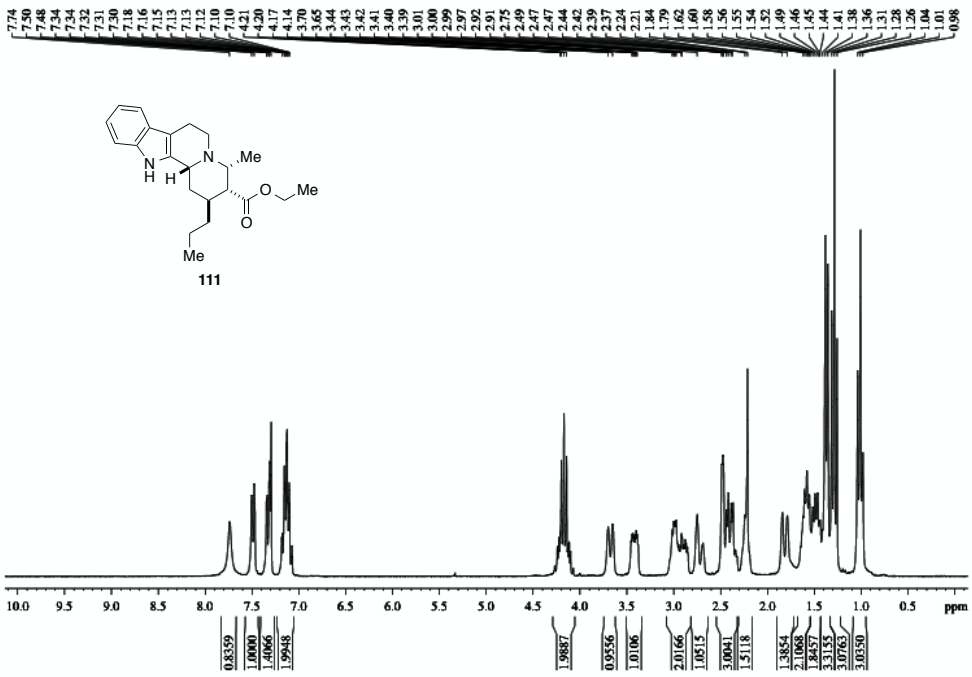
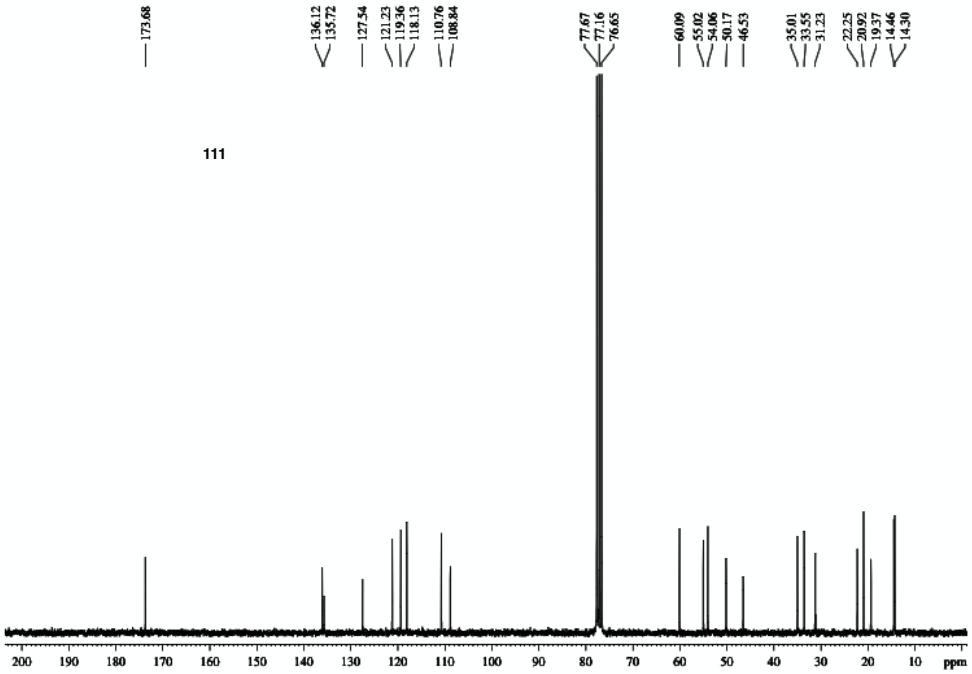
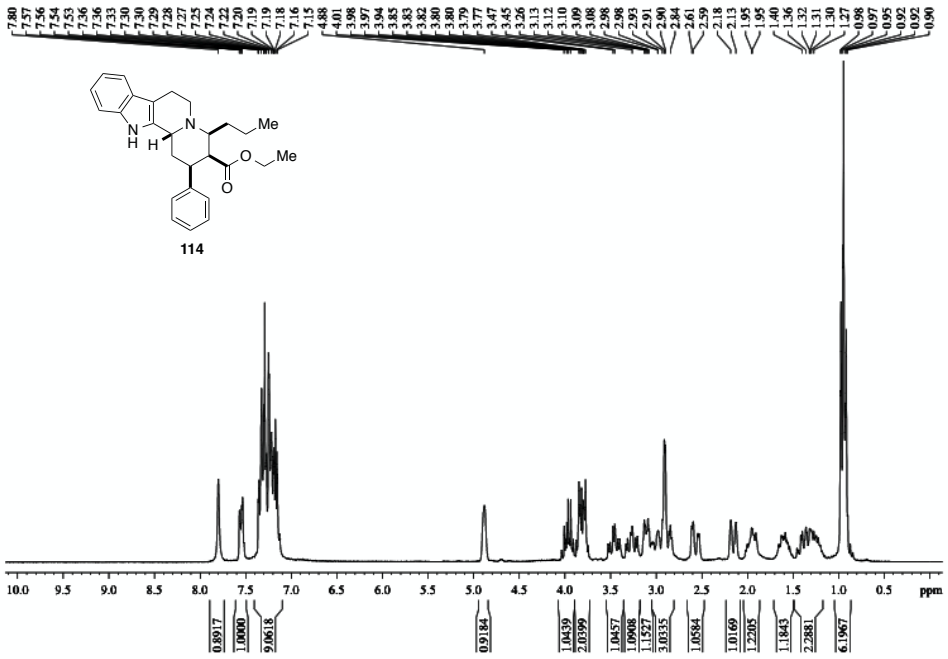
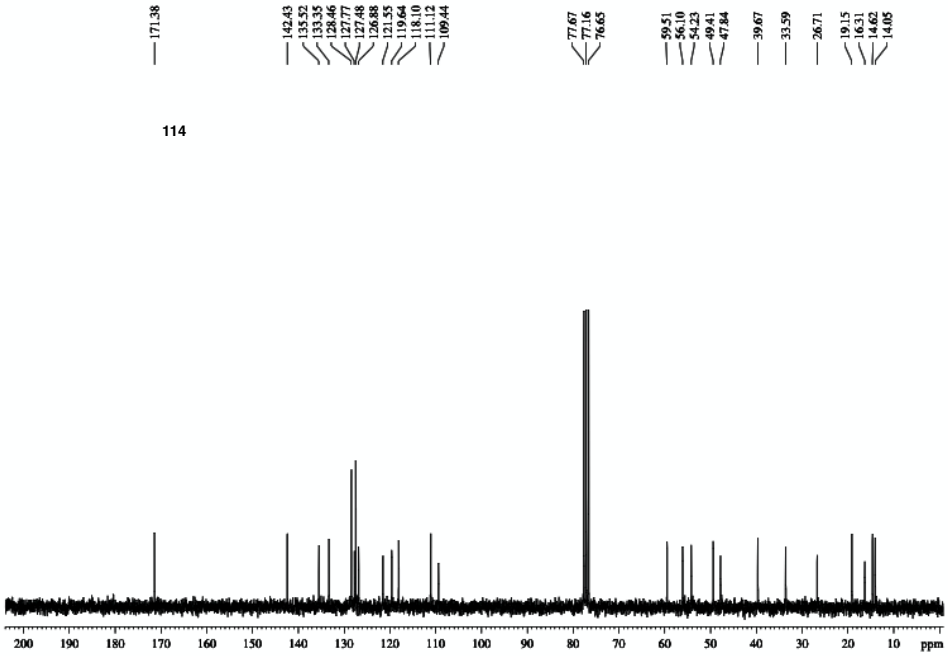
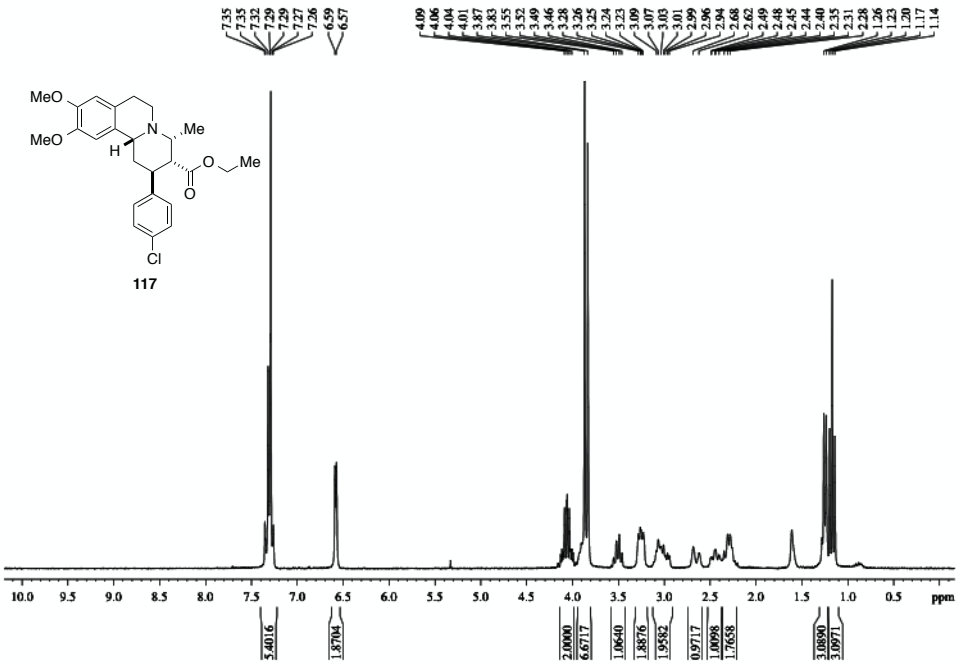

171.17
137.60 135.73 133.84 131.37 129.17 127.88 127.56 126.36 125.57 125.53 124.02 122.75 121.63 119.71 118.06 111.30 109.44
77.67 77.16 76.65
59.59 56.07 51.59 49.59 47.93
34.89
27.31
18.76 16.14 14.07
108
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

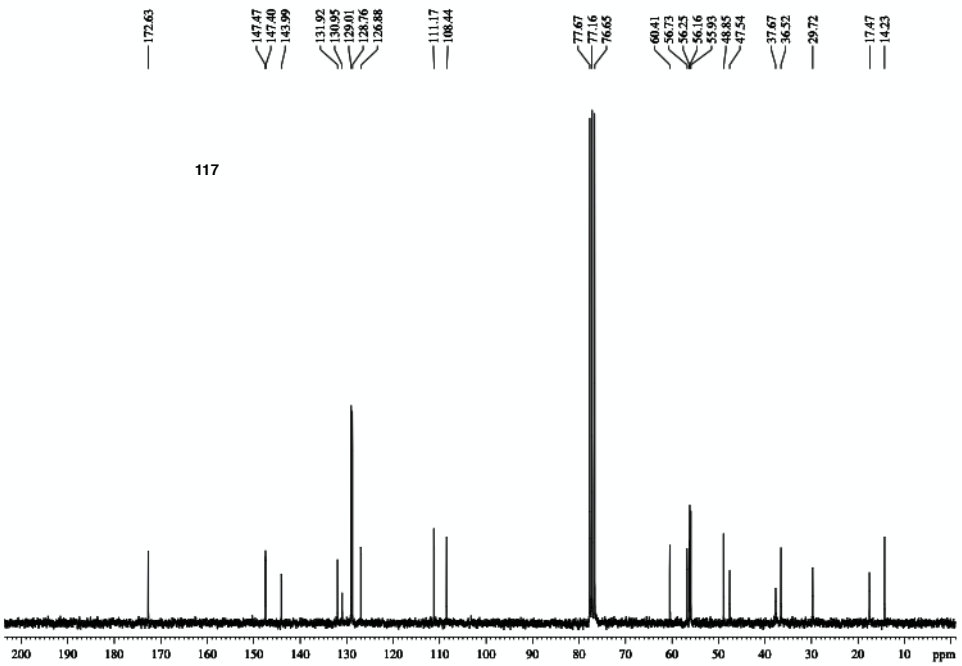

7.74 7.50 7.48 7.34 7.34 7.32 7.31 7.30 7.18 7.16 7.15 7.13 7.13 7.12 7.10 7.10 4.21 4.20 4.17 4.14 3.70 3.65 3.44 3.43 3.42 3.41 3.40 3.39 3.01 3.00 2.99 2.97 2.92 2.91 2.75 2.49 2.47 2.47 2.44 2.42 2.39 2.37 2.24 2.21 1.84 1.79 1.62 1.60 1.58 1.56 1.55 1.54 1.52 1.49 1.46 1.45 1.44 1.41 1.38 1.36 1.31 1.28 1.26 1.04 1.01 0.98
N
H
N
H
Me
O
O
Me
Me
111
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8359 1.0000 1.4066 1.9948 1.9887 0.9556 1.0106 2.0166 1.0515 3.0041 1.5118 1.3854 2.1068 1.8457 3.3155 1.0763 3.0350

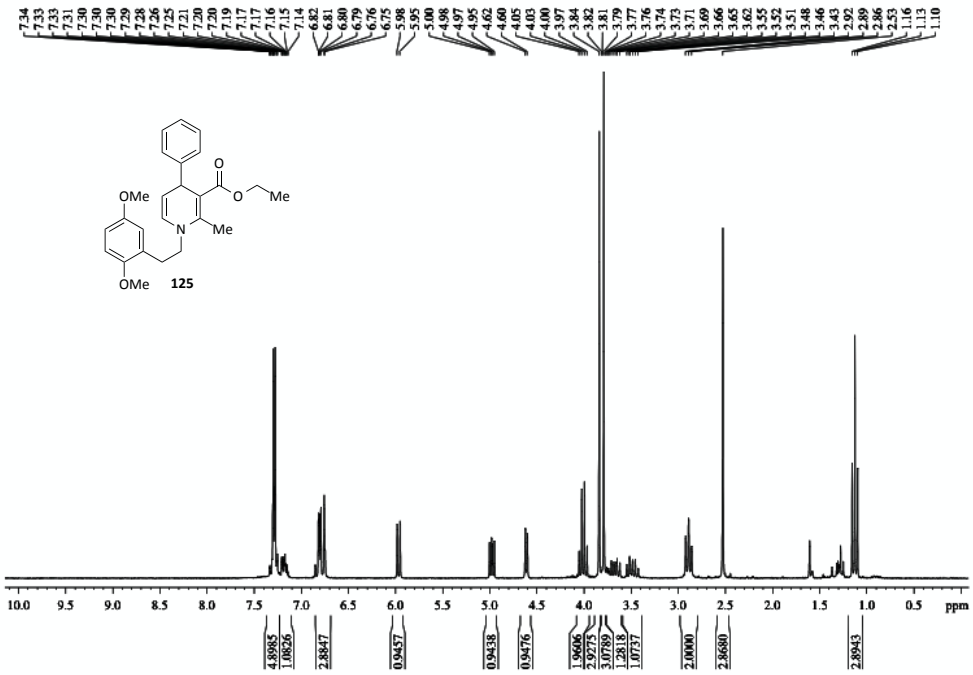

173.68
136.12 135.72 127.54 121.23 119.36 118.13 110.76 108.84
77.67 77.16 76.65
60.09 55.02 54.06 50.17 46.53
35.01 33.55 31.23 22.25 20.92 19.37 14.46 14.30
111
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

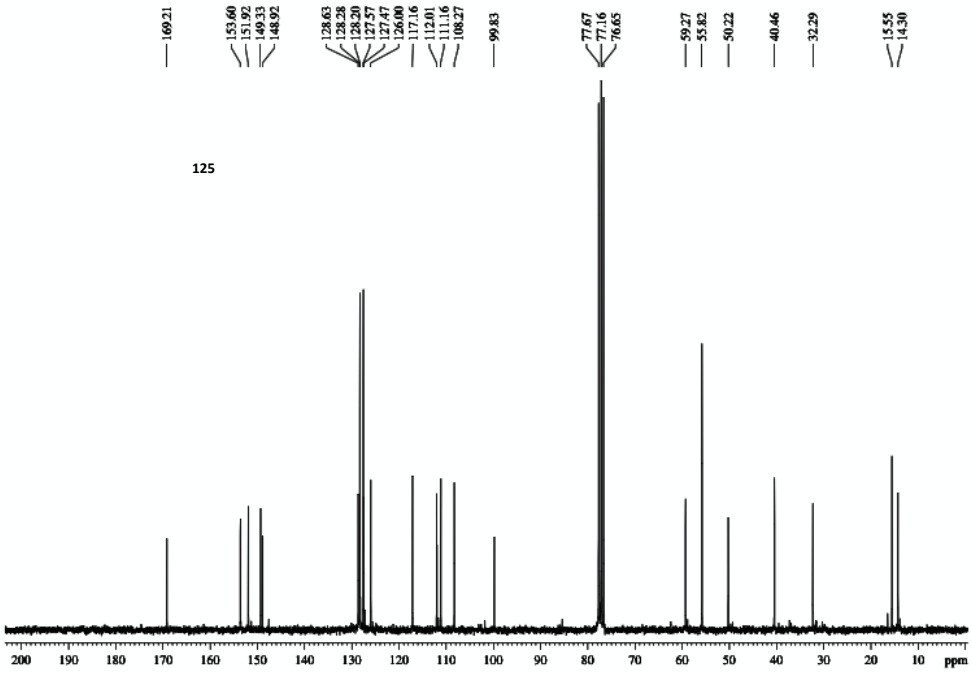

7.80 7.57 7.56 7.54 7.53 7.36 7.36 7.33 7.30 7.30 7.29 7.28 7.27 7.25 7.24 7.22 7.20 7.19 7.19 7.18 7.16 7.15 4.88 4.01 3.98 3.97 3.94 3.85 3.83 3.82 3.80 3.80 3.79 3.77 3.47 3.45 3.26 3.13 3.12 3.10 3.09 3.08 2.98 2.98 2.93 2.91 2.90 2.84 2.61 2.59 2.18 2.13 1.95 1.95 1.40 1.36 1.32 1.31 1.30 1.27 0.98 0.97 0.95 0.92 0.92 0.90
N
H
H
N
Me
O
Me
O
114
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8917 1.0000 9.0618 0.9184 1.0439 2.0399 1.0457 1.0908 1.1527 3.0335 1.0584 1.0169 1.2205 1.1843 2.2881 6.1967

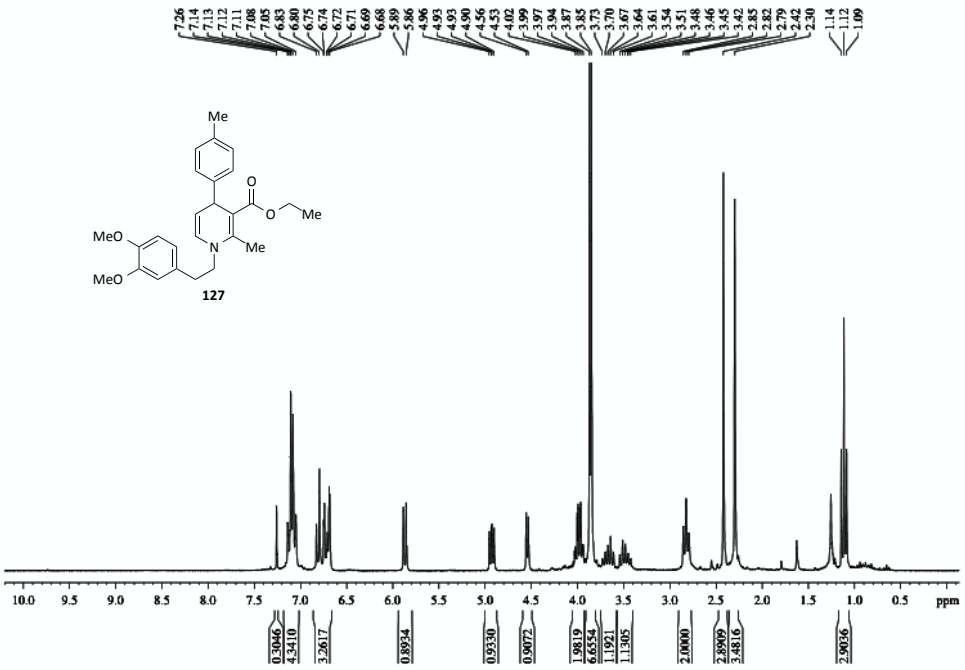

171.38
142.43 135.52 133.35 128.46 127.77 127.48 126.88 121.55 119.64 118.10 111.12 109.44
77.67 77.16 76.65
59.51 56.10 54.23 49.41 47.84 39.67 33.59 26.71 19.15 16.31 14.62 14.05
114
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

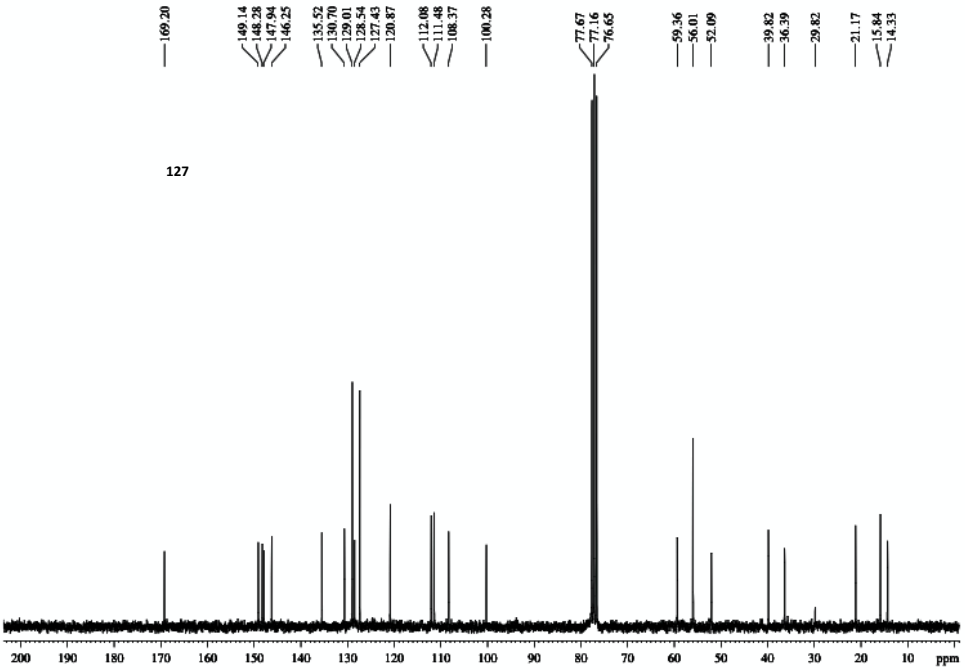

MeO
MeO
N
Me
H
O
Me
O
Cl
117
ppm


117
ppm


7.34 7.33 7.33 7.31 7.30 7.30 7.30 7.29 7.28 7.26 7.25 7.21 7.20 7.20 7.19 7.17 7.17 7.16 7.15 7.14 6.82 6.81 6.80 6.79 6.76 6.75 5.98 5.95 5.00 4.98 4.97 4.95 4.62 4.60 4.05 4.03 4.00 3.97 3.84 3.82 3.81 3.79 3.77 3.76 3.74 3.73 3.71 3.69 3.66 3.65 3.62 3.55 3.52 3.51 3.48 3.46 3.43 2.92 2.89 2.86 2.53 1.16 1.13 1.10
OMe
O
O
Me
N
Me
OMe
125
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.8985 1.0826 2.8847 0.9457 0.9438 0.9476 1.9666 2.9775 3.0789 1.2818 1.0737 2.0000 2.8680 2.8943


169.21 153.60 151.92 149.33 148.92 128.63 128.28 128.20 127.57 127.47 126.00 117.16 112.01 111.16 108.27 99.83 77.67 77.16 76.65 59.27 55.82 50.22 40.46 32.29 15.55 14.30
125
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.26
7.14
7.13
7.12
7.11
7.08
7.05
6.83
6.80
6.75
6.74
6.72
6.71
6.69
6.68
5.89
5.86
4.96
4.93
4.93
4.90
4.56
4.53
4.02
3.99
3.97
3.94
3.87
3.85
3.73
3.70
3.67
3.64
3.61
3.54
3.51
3.48
3.46
3.45
3.42
2.85
2.82
2.79
2.42
2.30
1.14
1.12
1.09
Me
O
O
Me
MeO
Me
N
MeO
127
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.3046
4.3410
3.2617
0.8934
0.9330
0.9072
1.9819
6.6554
1.1921
1.1305
2.0000
2.8909
3.4816
2.9036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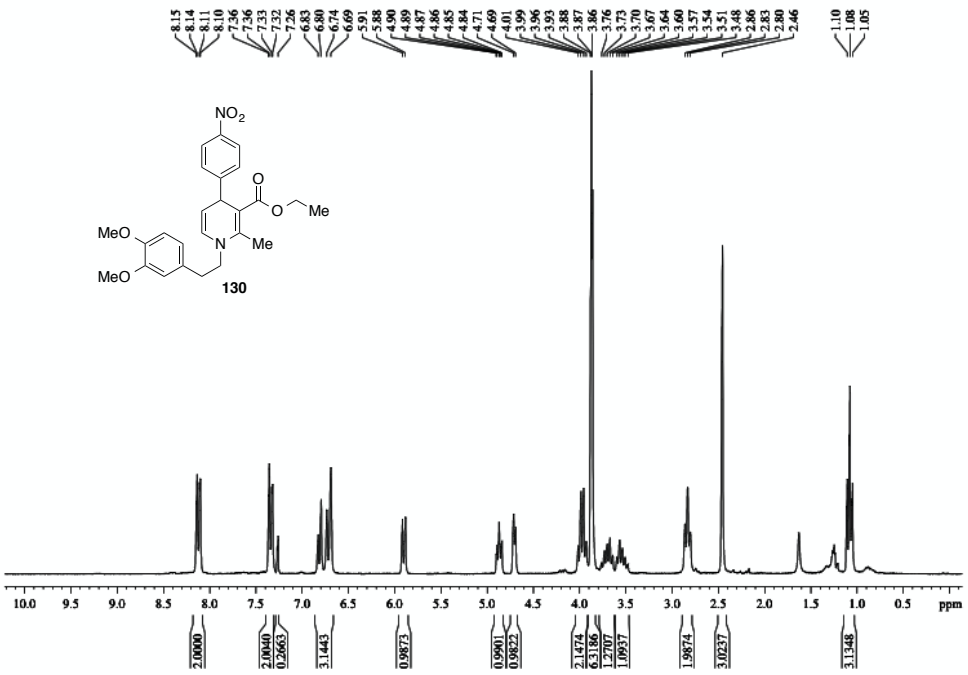
149.14
148.28
147.94
146.25
135.52
130.70
129.01
128.54
127.43
120.87
112.08
111.48
108.37
100.28
77.67
77.16
76.65
59.36
56.01
52.09
39.82
36.39
29.82
21.17
15.84
14.33
127
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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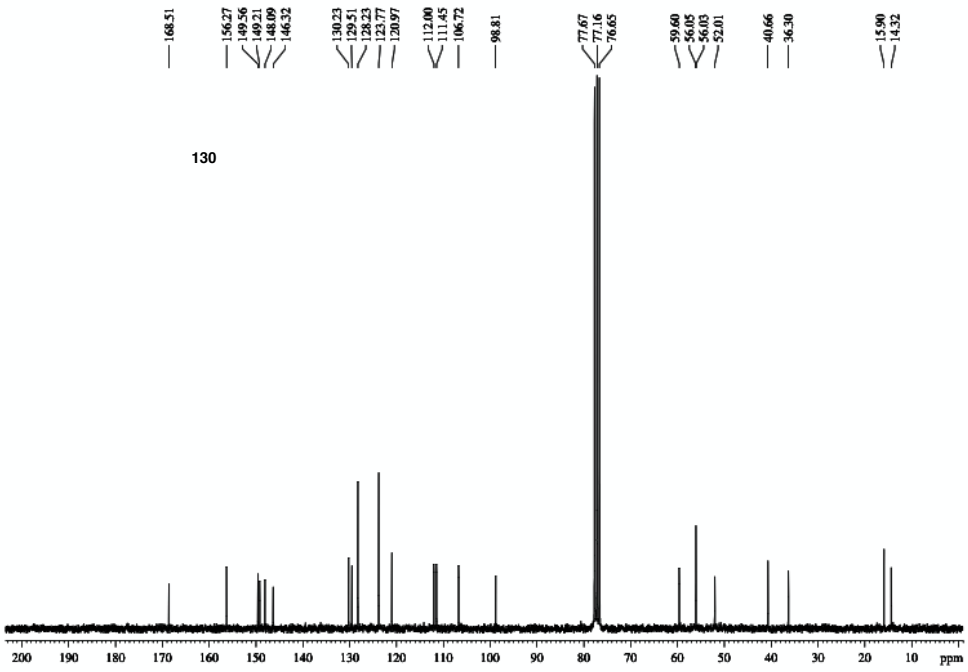
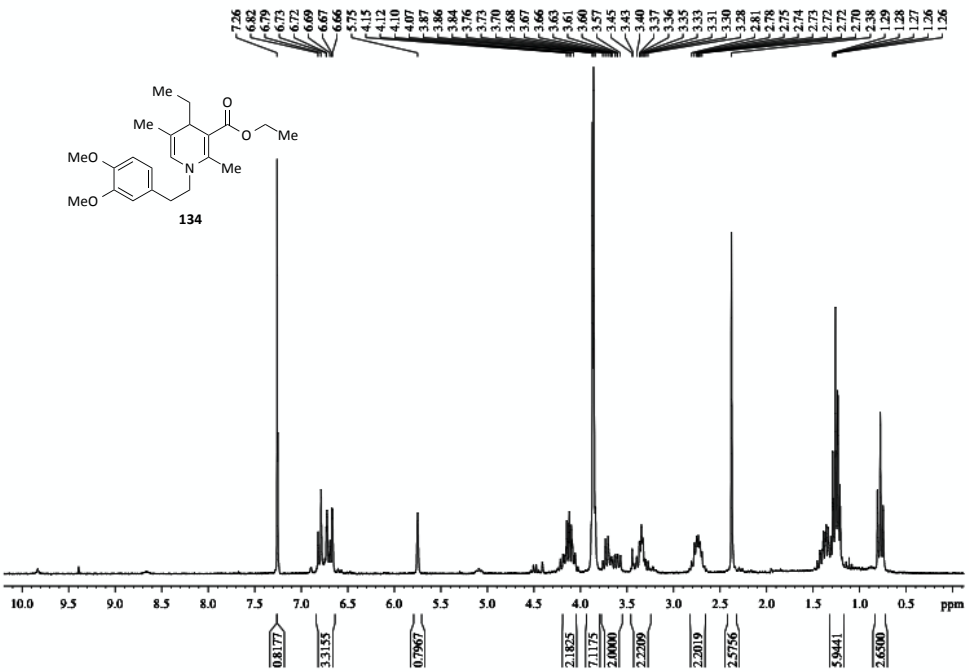
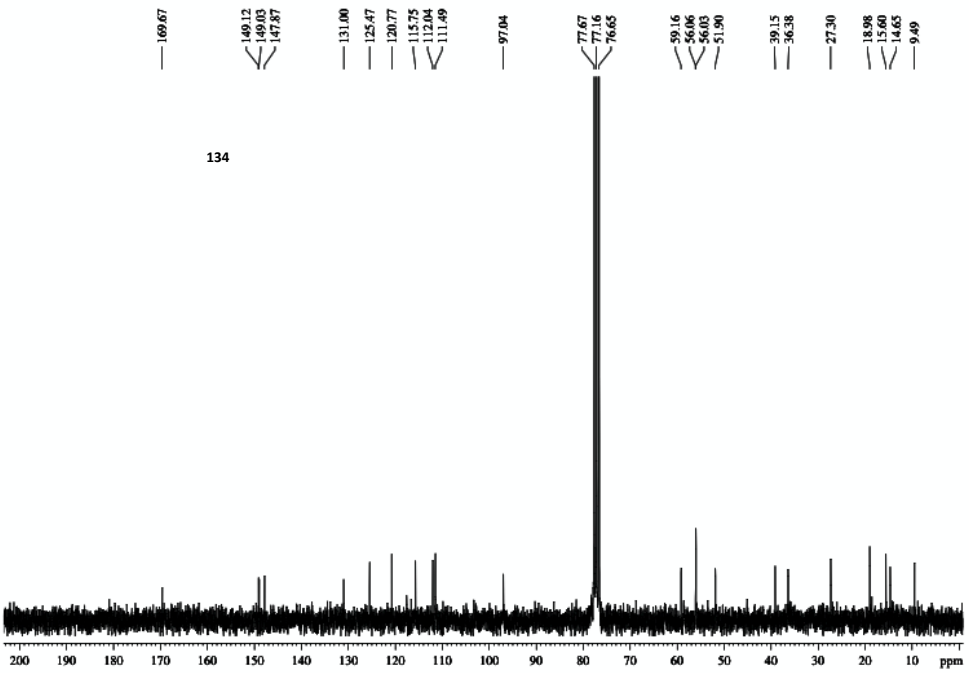
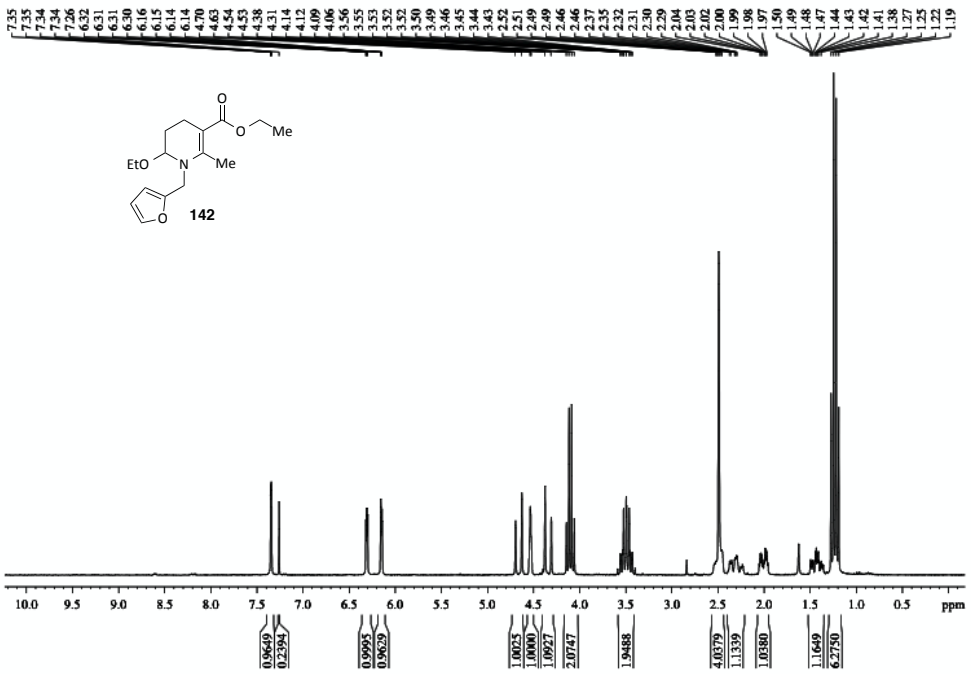
8.14
8.11
8.10
7.36
7.36
7.33
7.33
7.26
6.83
6.80
6.74
6.69
5.91
5.88
4.90
4.89
4.87
4.86
4.85
4.84
4.71
4.69
4.01
3.99
3.96
3.93
3.88
3.87
3.86
3.76
3.73
3.70
3.67
3.64
3.60
3.57
3.54
3.51
3.48
2.86
2.83
2.80
2.46
1.10
1.08
1.05
NO2
O
O
Me
MeO
N
Me
MeO
130
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.0000
2.0040
0.2663
3.1443
0.9873
0.9901
0.9822
2.1474
6.3186
1.2707
1.0937
1.9874
3.0237
3.1348


168.51
156.27
149.56
149.21
148.09
146.32
130.23
129.51
128.23
123.77
120.97
112.00
111.45
106.72
98.81
77.67
77.16
76.65
59.60
56.05
56.03
52.01
40.66
36.30
15.90
14.32
130
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Me
Me
O
O
Me
MeO
MeO
N
Me
134
ppm


134
ppm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7.34
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6.32
6.31
6.31
6.30
6.16
6.15
6.14
6.14
4.70
4.63
4.54
4.53
4.38
4.31
4.14
4.12
4.09
4.06
3.56
3.55
3.53
3.52
3.52
3.50
3.49
3.46
3.45
3.44
3.43
2.52
2.51
2.49
2.49
2.46
2.46
2.37
2.35
2.32
2.31
2.30
2.29
2.04
2.03
2.02
2.00
1.99
1.98
1.97
1.50
1.49
1.48
1.47
1.44
1.43
1.42
1.41
1.38
1.27
1.25
1.22
1.19
O
O
Me
EtO
N
Me
O
142
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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0.2394
0.9995
0.9629
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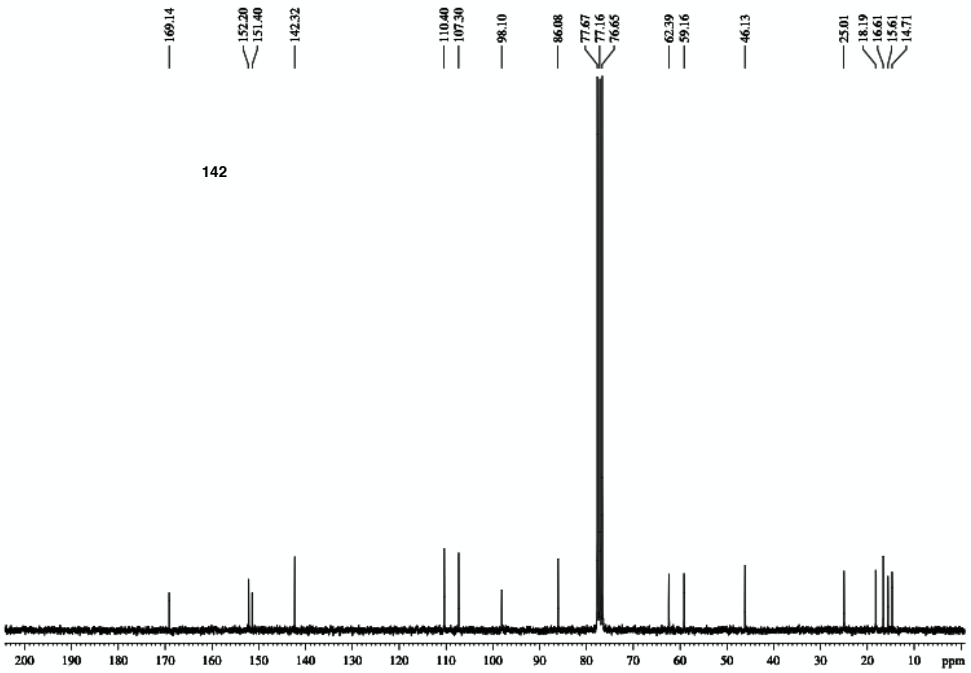
2.0747
1.9488
4.0379
1.1339
1.0380
1.1649
6.2750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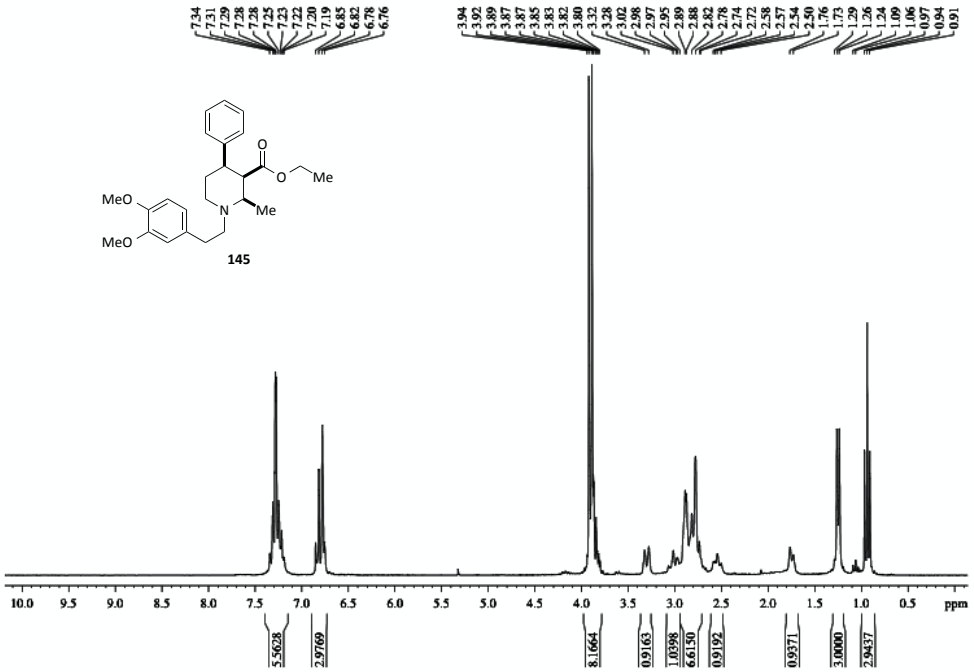
151.40
142.32
110.40
107.30
98.10
86.08
77.67
77.16
76.65
62.39
59.16
46.13
25.01
18.19
16.61
15.61
14.71
142
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.29
7.28
7.28
7.25
7.23
7.22
7.20
7.19
6.85
6.82
6.78
6.76
3.94
3.92
3.89
3.87
3.87
3.85
3.83
3.82
3.80
3.32
3.28
3.02
2.98
2.97
2.95
2.89
2.88
2.82
2.78
2.74
2.72
2.58
2.57
2.54
2.50
1.76
1.73
1.29
1.26
1.24
1.09
1.06
0.97
0.94
0.91
O
O
Me
MeO
N
Me
MeO
145
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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8.1664
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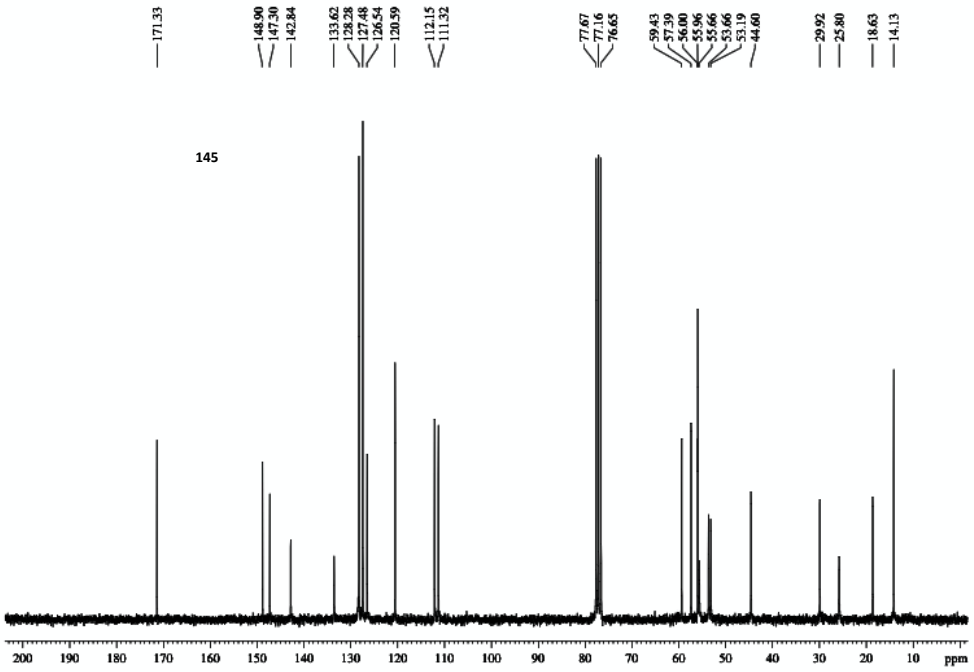
1.0398
6.6150
0.9192
0.9371
3.0000
2.9437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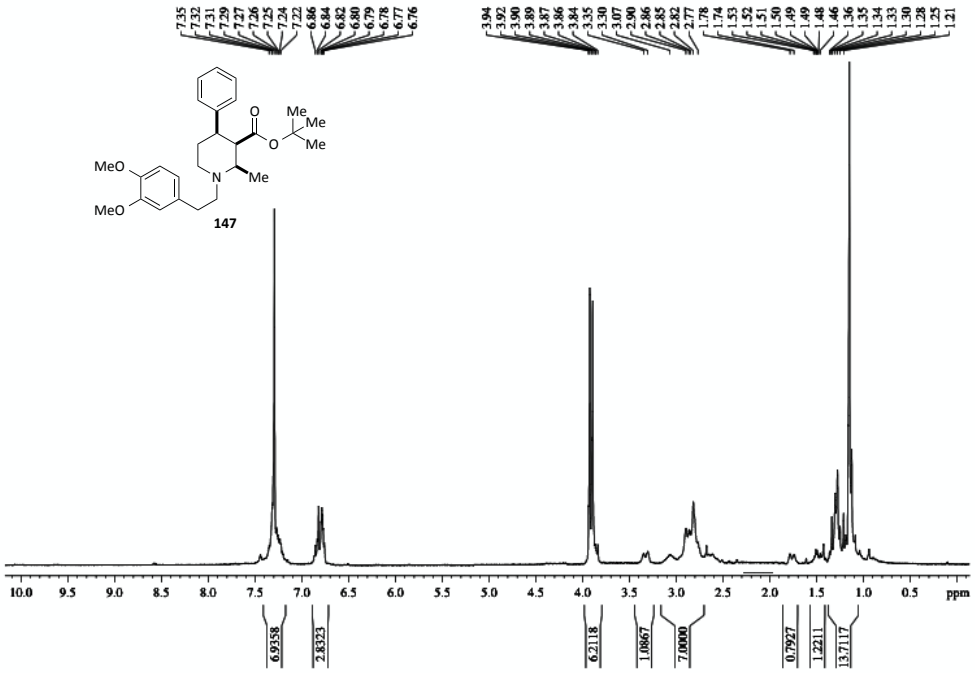
142.84
133.62
128.28
127.48
126.54
120.59
112.15
111.32
77.67
77.16
76.65
59.43
57.39
56.00
55.96
55.66
53.66
53.19
44.60
29.92
25.80
18.63
14.13
145
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.32
7.31
7.29
7.27
7.26
7.25
7.24
7.22
6.86
6.84
6.82
6.80
6.79
6.78
6.77
6.76
3.94
3.92
3.90
3.89
3.87
3.86
3.84
3.35
3.30
3.07
2.90
2.86
2.85
2.82
2.77
1.78
1.74
1.55
1.52
1.51
1.50
1.49
1.49
1.48
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1.36
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1.34
1.33
1.30
1.28
1.25
1.21
MeO
MeO
N
O
O
Me
Me
Me
Me
147
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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6.2118
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7.0000
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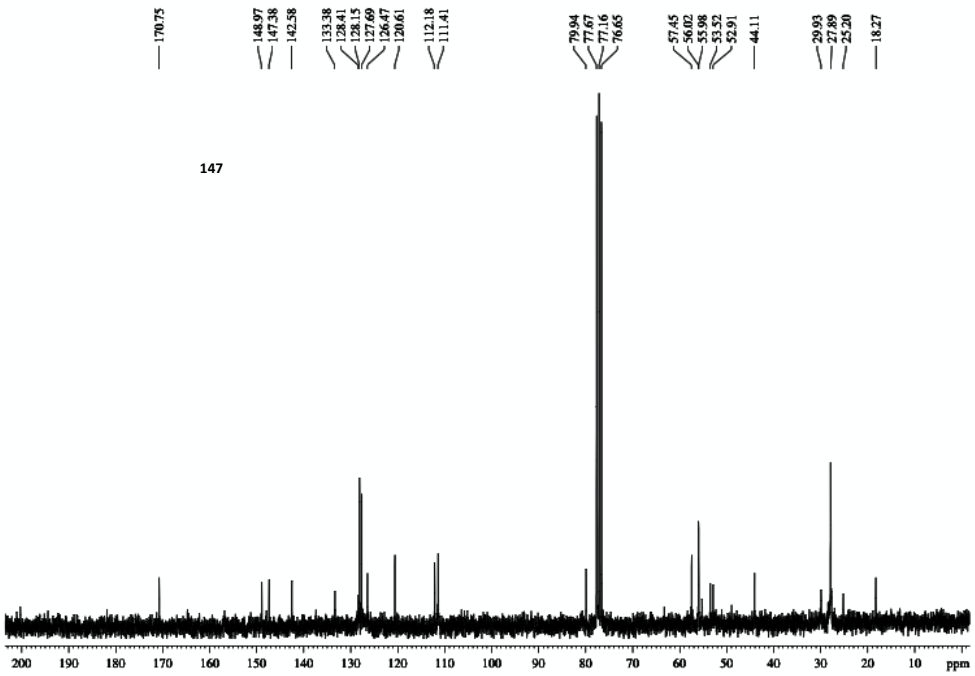
1.2211
13.7117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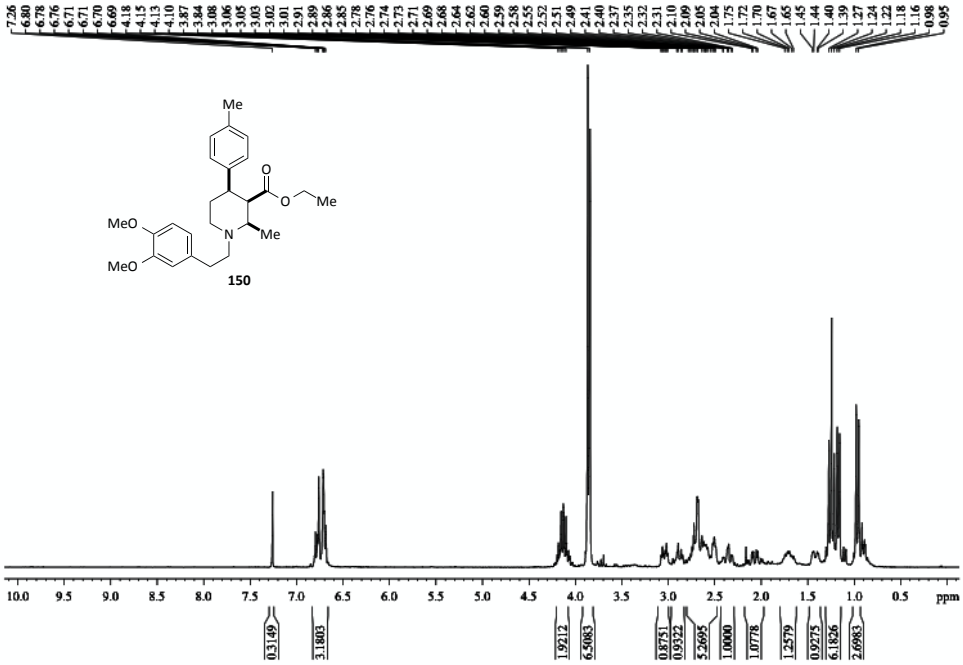
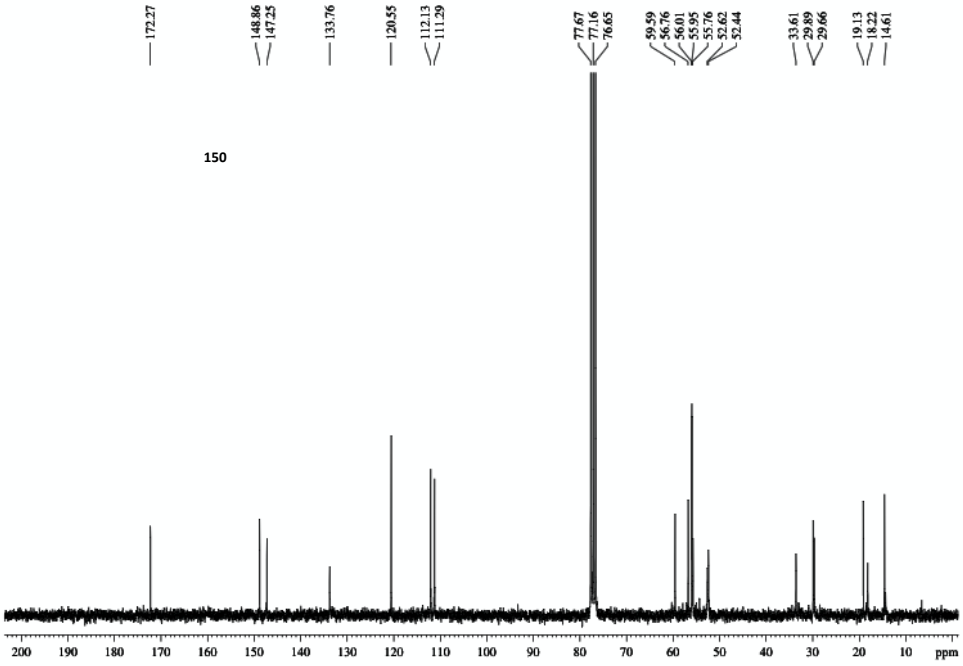
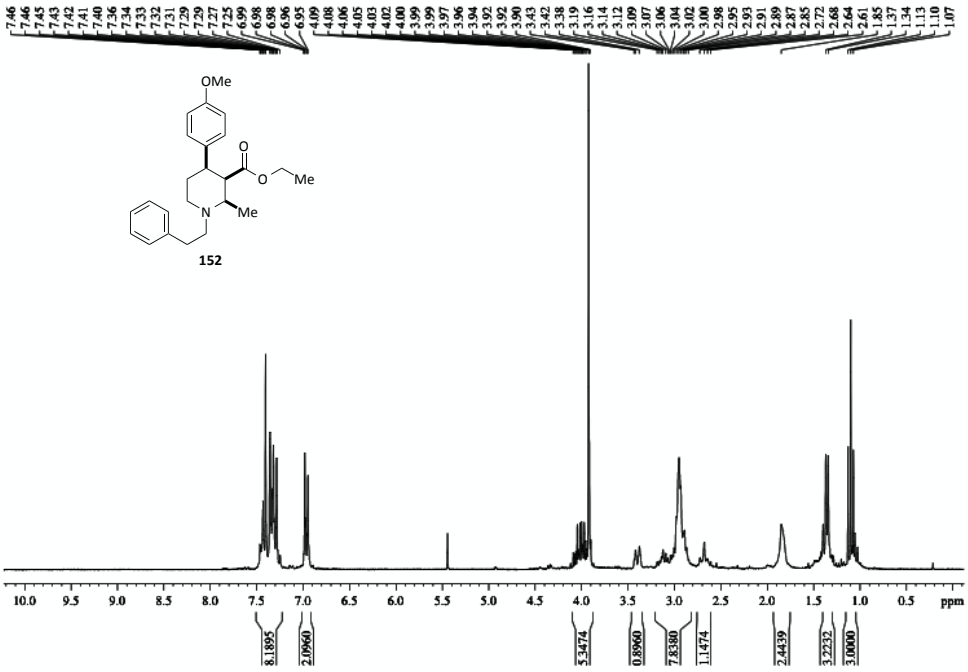
142.58
133.38
128.41
128.15
127.69
126.47
120.61
112.18
111.41
79.94
77.67
77.16
76.65
57.45
56.02
55.98
53.52
52.91
44.11
29.93
27.89
25.20
18.27
147
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Me
O
O
Me
MeO
MeO
N
Me
150


150


OMe
O
O
Me
N
Me
152
ppm
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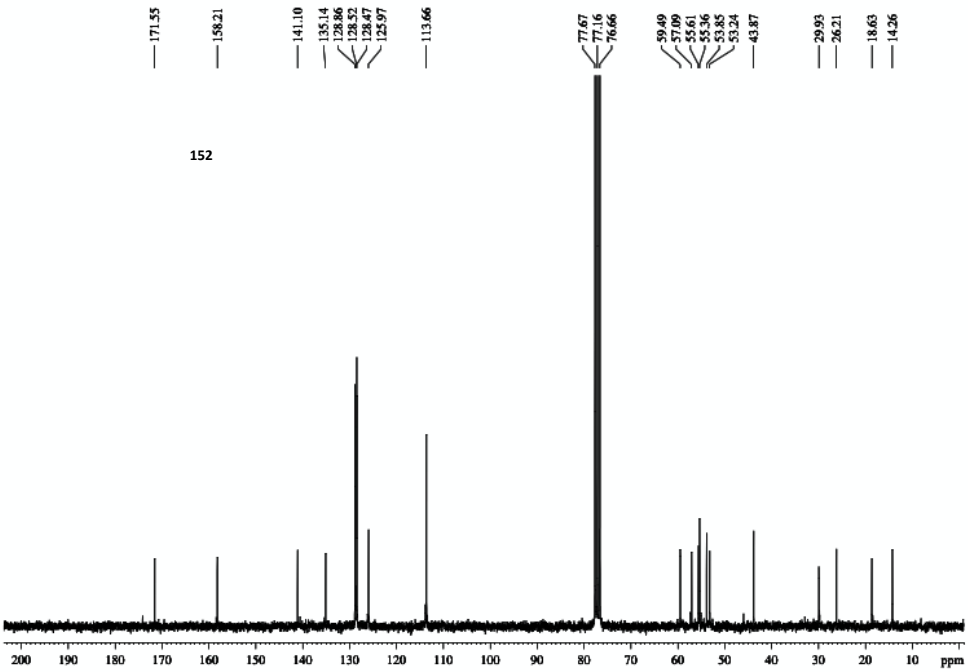
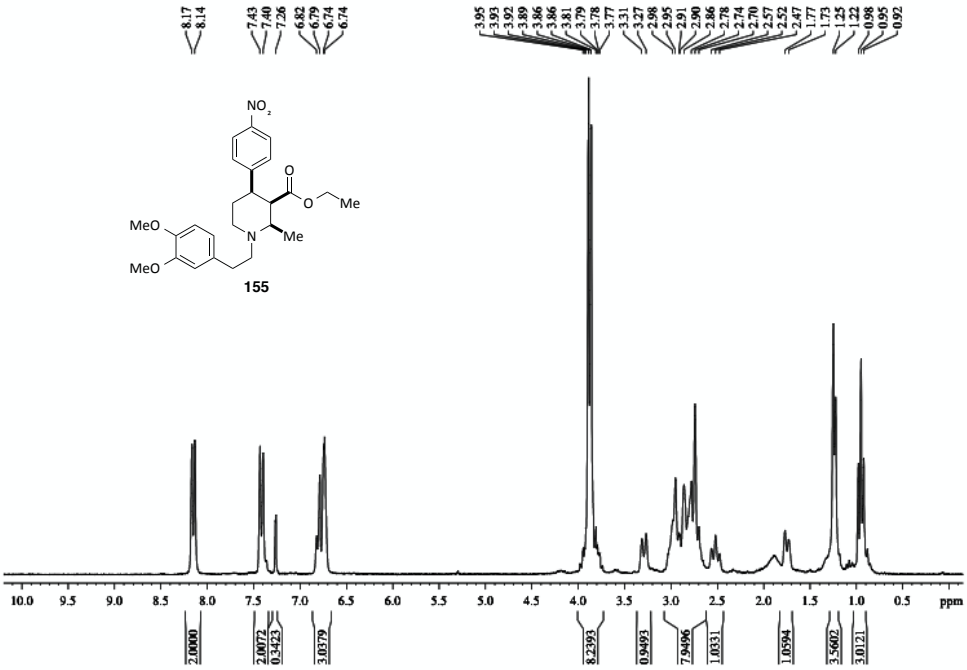
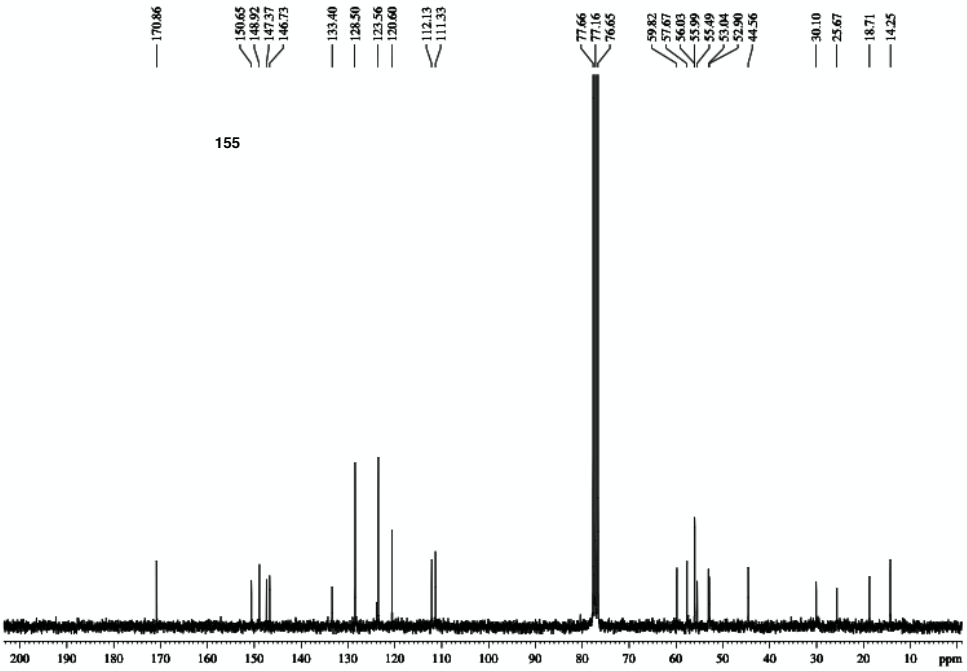
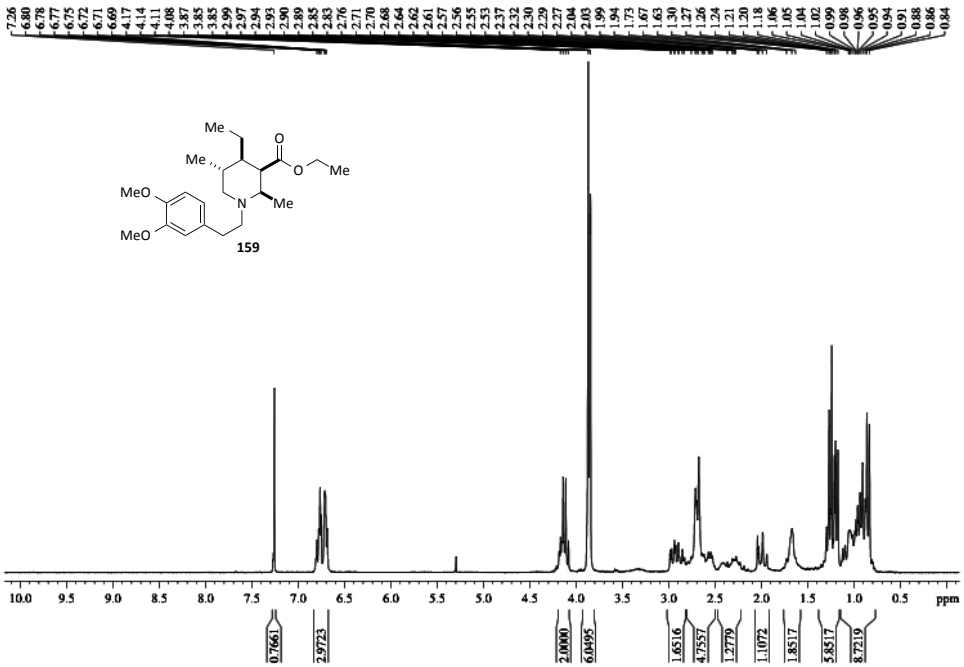
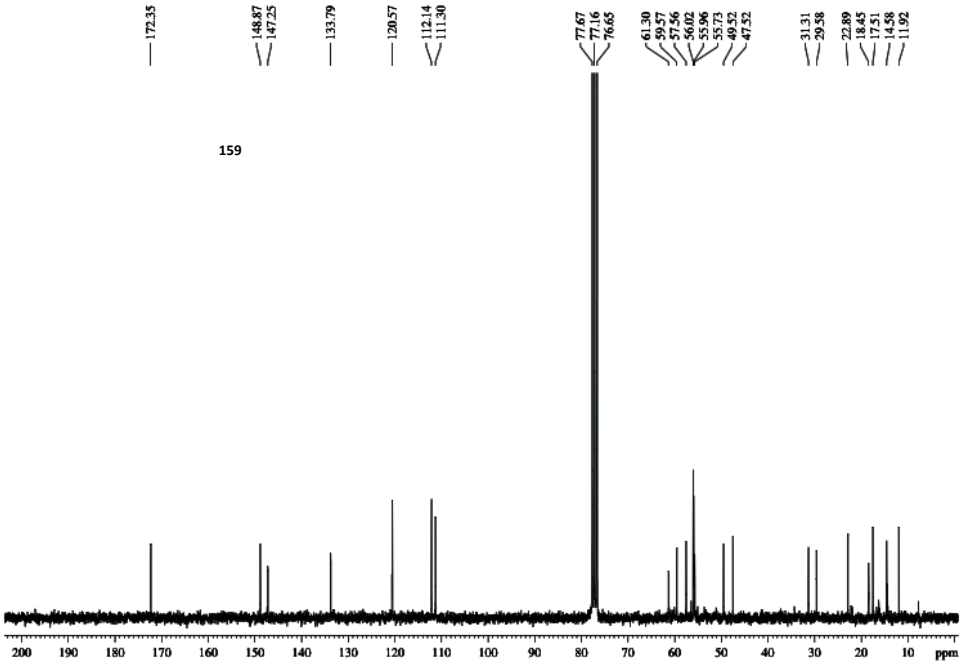
2.0960
5.3474
0.8960
7.8380
1.1474
2.4439
3.2232
3.0000

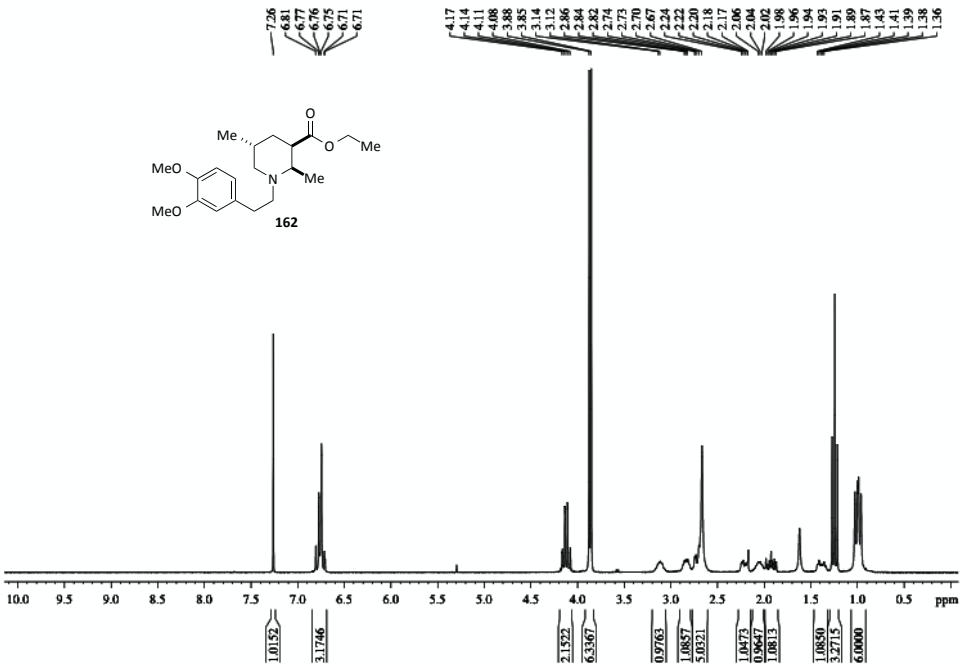

171.55
158.21
141.10
135.14
128.86
128.52
128.47
125.97
113.66
77.67
77.16
76.66
59.49
57.09
55.61
55.36
53.85
53.24
43.87
29.93
26.21
18.63
14.26
152
ppm


8.17
8.14
7.43
7.40
7.26
6.82
6.79
6.74
6.74
3.95
3.93
3.92
3.89
3.86
3.86
3.81
3.79
3.78
3.77
3.31
3.27
2.98
2.95
2.91
2.90
2.86
2.78
2.74
2.70
2.57
2.52
2.47
1.77
1.73
1.25
1.22
0.98
0.95
0.92
NO2
O
O
Me
MeO
MeO
N
Me
155
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.0000
2.0072
0.3423
3.0379
8.2393
0.9493
7.9496
1.0331
1.0594
3.5602
3.0121


170.86
150.65
148.92
147.37
146.73
133.40
128.50
123.56
120.60
112.13
111.33
77.66
77.16
76.65
59.82
57.67
56.03
55.99
55.49
53.04
52.90
44.56
30.10
25.67
18.71
14.25
155
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.26
6.80
6.78
6.77
6.75
6.72
6.71
6.69
4.17
4.14
4.11
4.08
3.87
3.85
3.85
3.85
2.99
2.97
2.94
2.93
2.90
2.89
2.85
2.83
2.76
2.71
2.70
2.68
2.64
2.62
2.61
2.57
2.56
2.55
2.53
2.37
2.32
2.30
2.29
2.27
2.04
2.03
1.99
1.94
1.73
1.67
1.63
1.30
1.27
1.26
1.24
1.21
1.20
1.18
1.06
1.05
1.04
1.02
0.99
0.98
0.96
0.95
0.94
0.91
0.88
0.86
0.84
Me
O
Me
O
Me
MeO
N
Me
MeO
159
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.7661
2.9723
2.0000
6.0495
1.6516
4.7557
1.2779
1.1072
1.8517
5.8517
8.7219


172.35
148.87
147.25
133.79
120.57
112.14
111.30
77.67
77.16
76.65
61.30
59.57
57.56
56.02
55.96
55.73
49.52
47.52
31.31
29.58
22.89
18.45
17.51
14.58
11.92
159
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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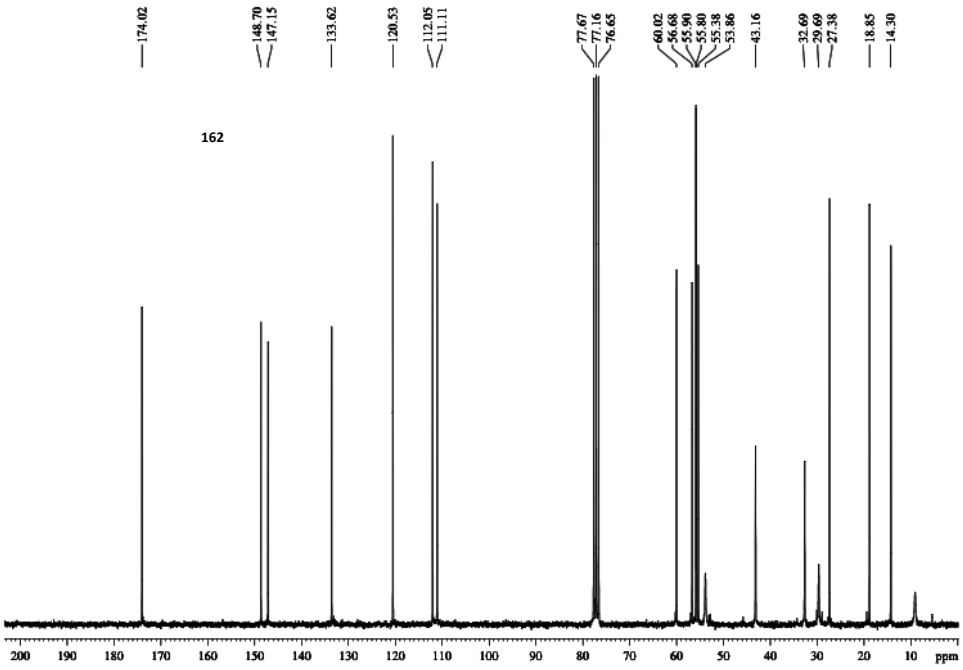
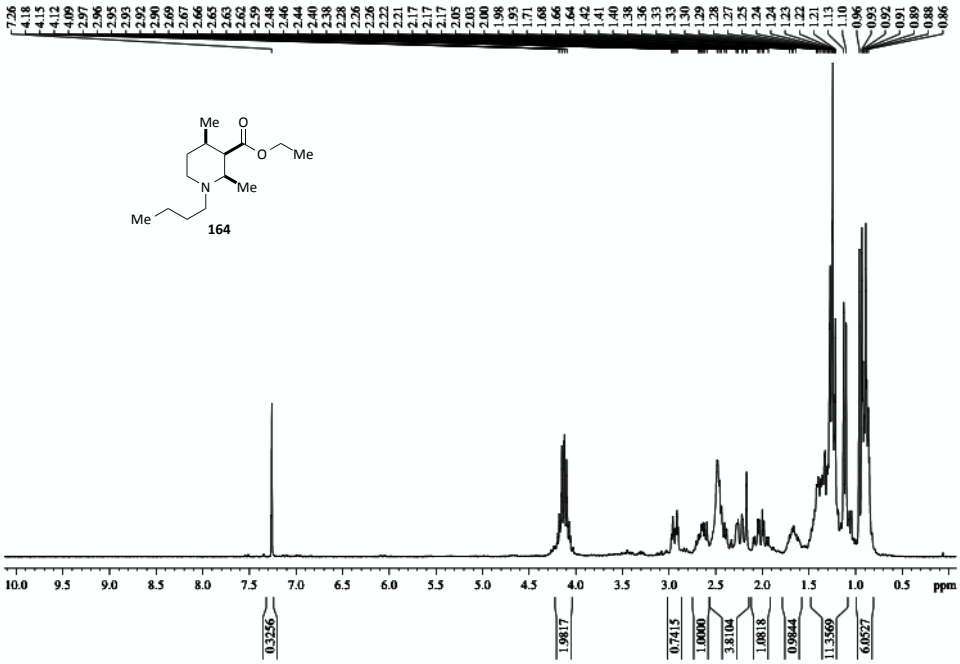
6.81
6.77
6.76
6.75
6.71
6.71
4.17
4.14
4.11
4.08
3.88
3.85
3.14
3.12
2.86
2.84
2.82
2.74
2.73
2.70
2.67
2.24
2.22
2.20
2.18
2.17
2.06
2.04
2.02
1.98
1.96
1.94
1.93
1.91
1.89
1.87
1.43
1.41
1.39
1.38
1.36
Me
O
O
Me
MeO
N
Me
MeO
162
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0152
3.1746
2.1522
6.3367
0.9763
1.0857
5.0921
1.0473
0.9647
1.0813
1.0850
3.2715
6.0000


174.02
148.70
147.15
133.62
120.53
112.05
111.11
77.67
77.16
76.65
60.02
56.68
55.90
55.80
55.38
53.86
43.16
32.69
29.69
27.38
18.85
14.30
162
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Me
O
O
Me
N
Me
Me
164
ppm
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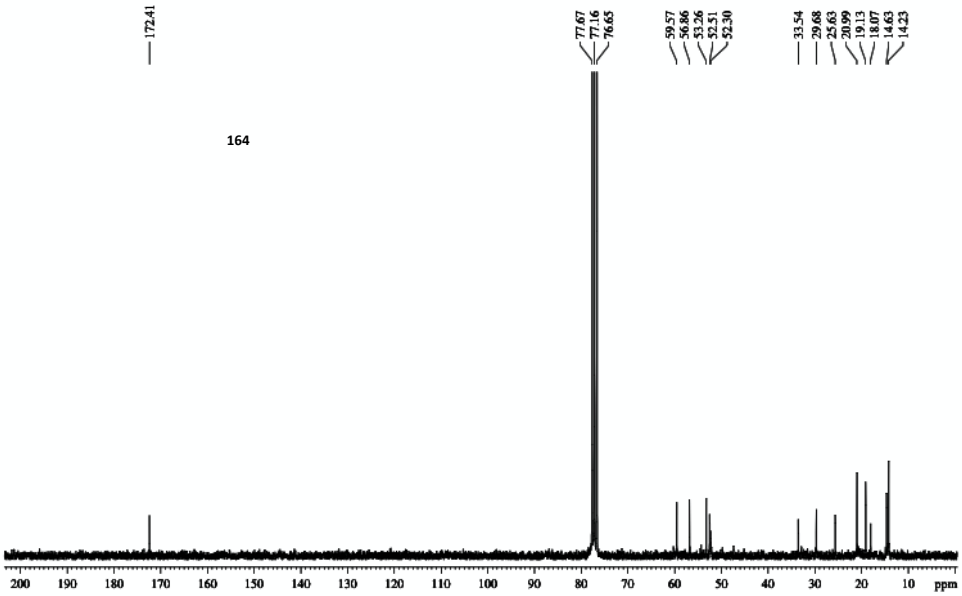
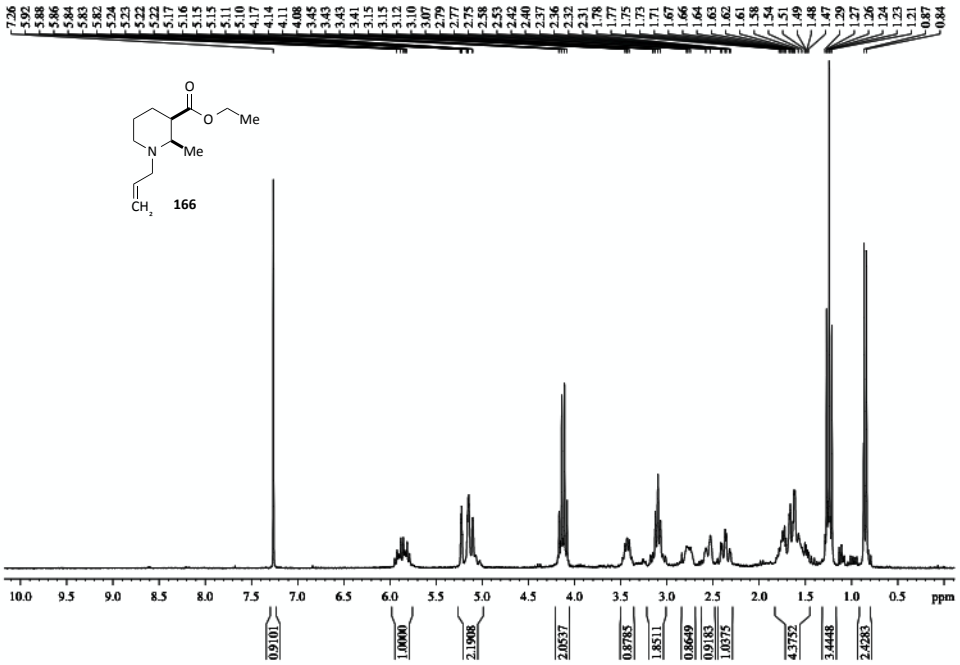
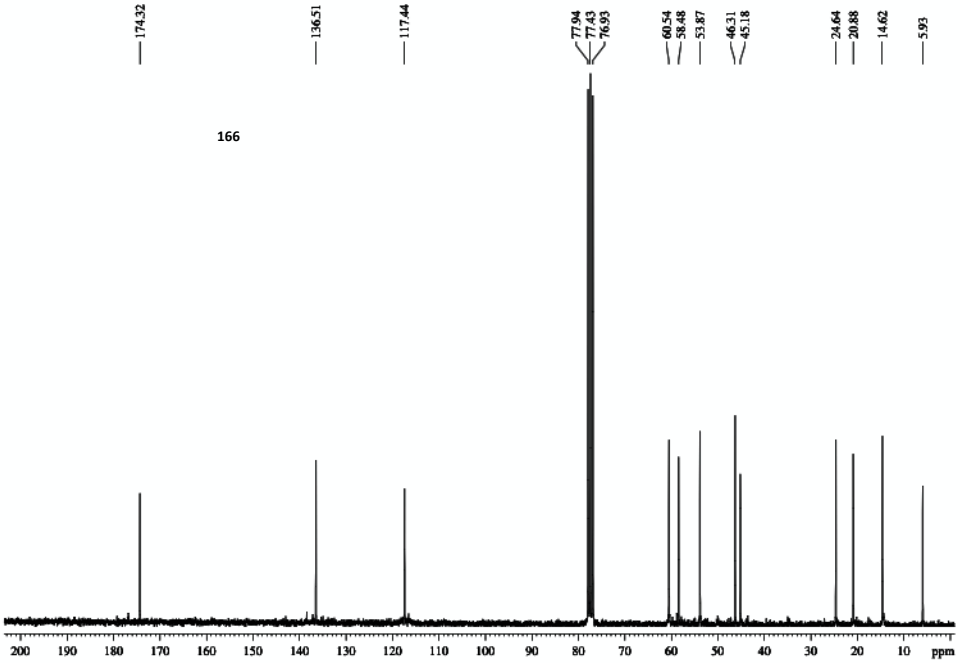
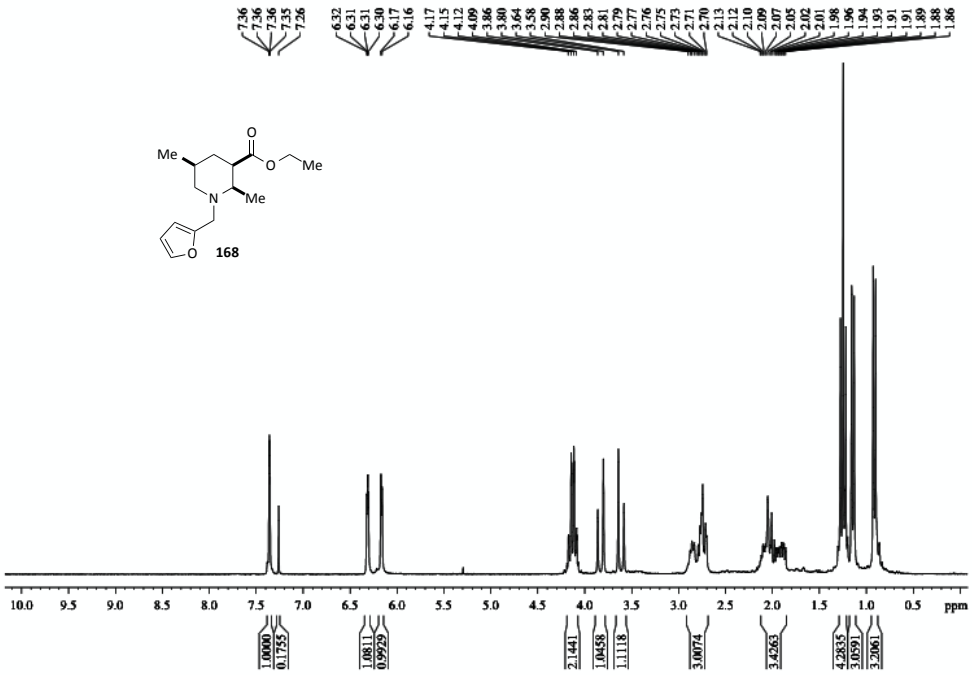
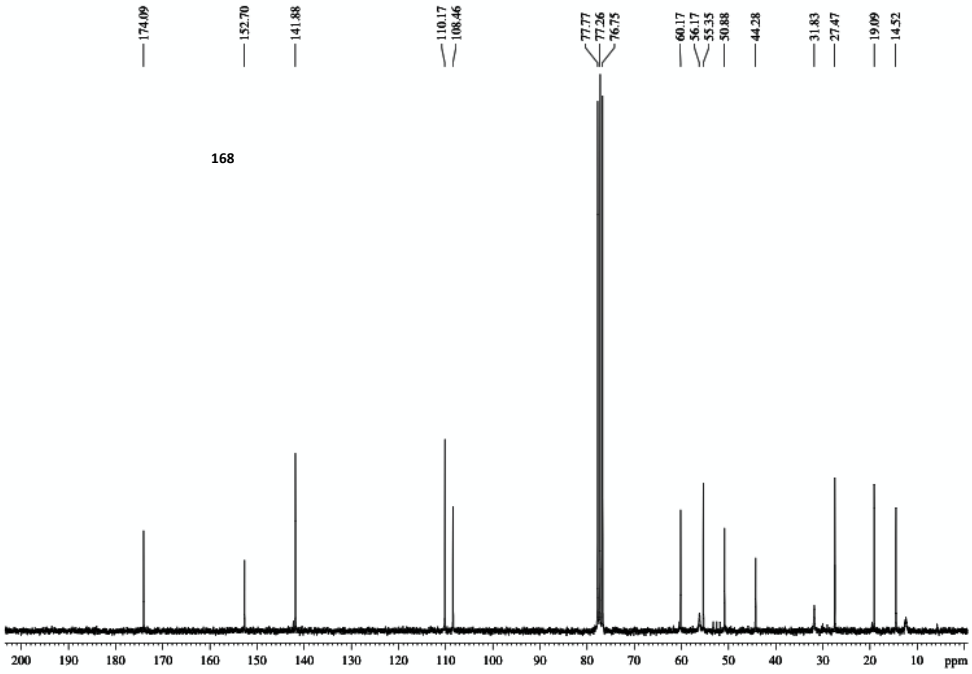
1.9817
0.7415
1.0000
3.8104
1.0818
0.9844
1.3569
6.0527


172.41
77.67
77.16
76.65
59.57
56.86
53.26
52.51
52.30
33.54
29.68
25.63
20.99
19.13
18.07
14.63
14.23
164
ppm


7.26
5.92
5.88
5.86
5.84
5.83
5.82
5.24
5.23
5.22
5.22
5.17
5.16
5.15
5.15
5.11
5.10
4.17
4.14
4.11
4.08
3.45
3.43
3.43
3.41
3.15
3.15
3.12
3.10
3.07
2.79
2.77
2.75
2.58
2.53
2.42
2.40
2.37
2.36
2.32
2.31
1.78
1.77
1.75
1.73
1.71
1.67
1.66
1.64
1.63
1.62
1.61
1.58
1.54
1.51
1.49
1.48
1.47
1.29
1.27
1.26
1.24
1.23
1.21
0.87
0.84
O
O
Me
N
Me
CH2
166
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.9101
1.0000
2.1908
2.0537
0.8785
1.8511
0.8649
0.9183
1.0375
4.3752
3.4448
2.4283


174.32
136.51
117.44
77.94
77.43
76.93
60.54
58.48
53.87
46.31
45.18
24.64
20.88
14.62
5.93
166
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.36
7.36
7.36
7.35
7.26
6.32
6.31
6.31
6.30
6.17
6.16
4.17
4.15
4.12
4.09
3.86
3.80
3.64
3.58
2.90
2.88
2.86
2.83
2.81
2.79
2.77
2.76
2.75
2.73
2.71
2.70
2.13
2.12
2.10
2.09
2.07
2.05
2.02
2.01
1.98
1.96
1.94
1.93
1.91
1.91
1.89
1.88
1.86
Me
O
O
Me
N
Me
O
168
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000
0.1755
1.0811
0.9929
2.1441
1.0458
1.1118
3.0074
3.4263
4.2835
3.0591
2.2061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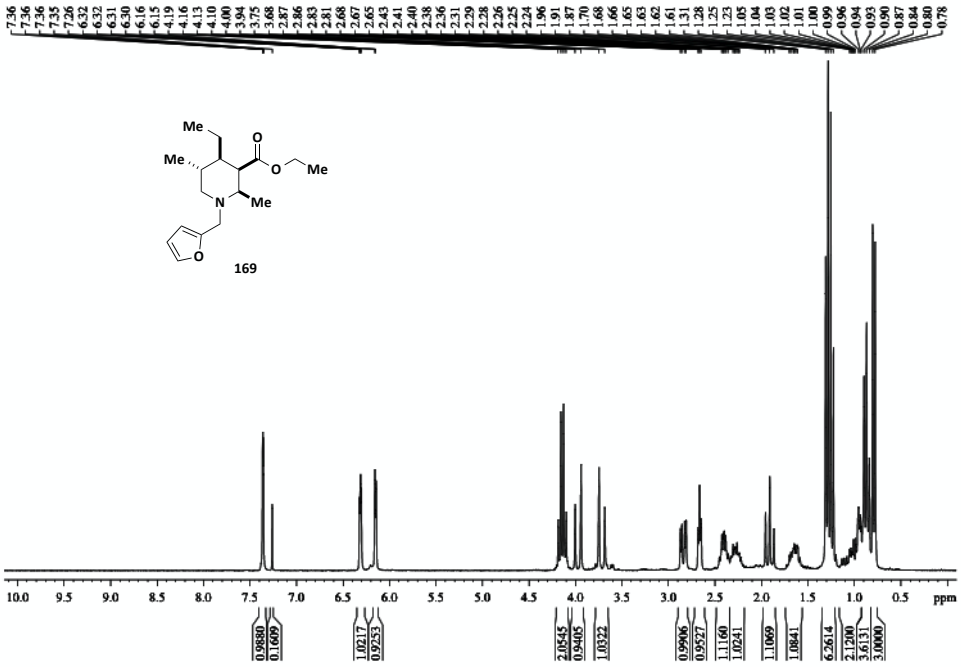
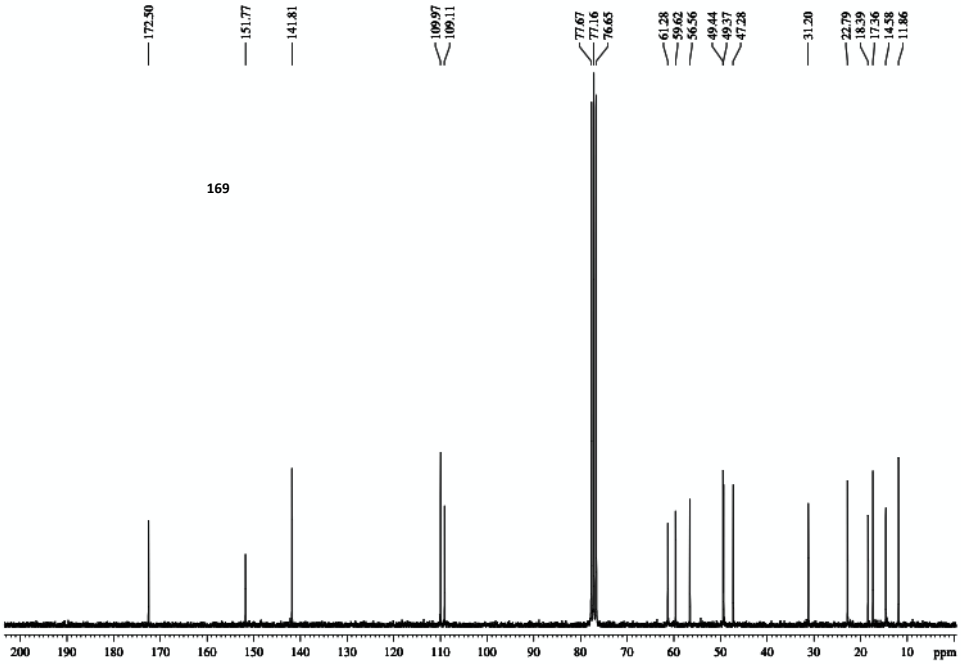
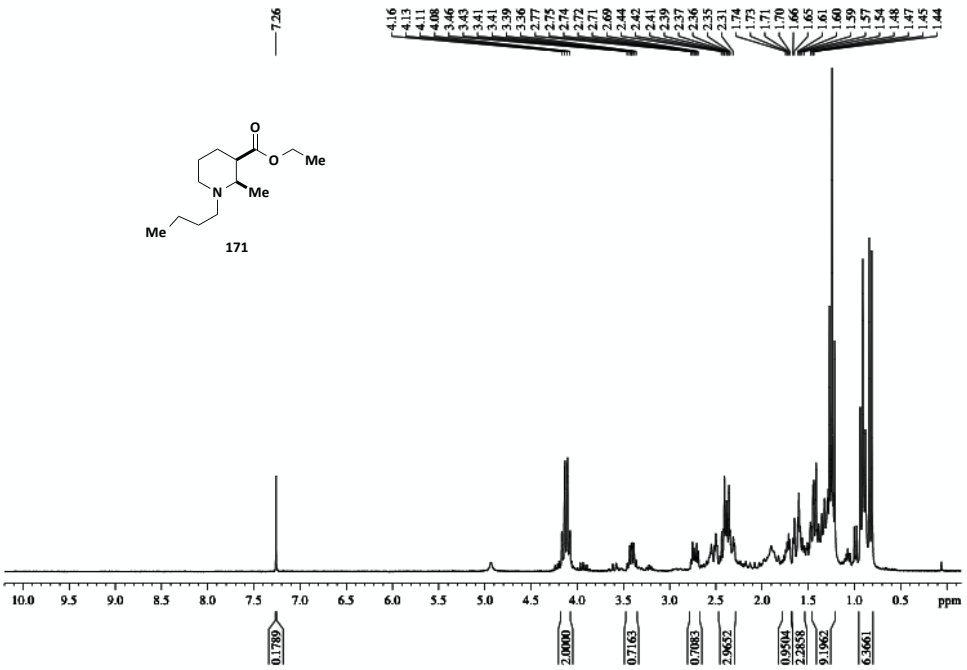
152.70
141.88
110.17
108.46
77.77
77.26
76.75
60.17
56.17
55.35
50.88
44.28
31.83
27.47
19.09
14.52
168
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Me
Me
O
O
Me
N
Me
O
169
ppm


169
ppm


7.26
4.16
4.13
4.11
4.08
3.46
3.43
3.41
3.41
3.39
3.36
2.77
2.75
2.74
2.72
2.71
2.69
2.44
2.42
2.41
2.39
2.37
2.36
2.35
2.31
1.74
1.73
1.71
1.70
1.66
1.65
1.61
1.60
1.59
1.57
1.54
1.48
1.47
1.45
1.44
O
O
Me
N
Me
Me
171
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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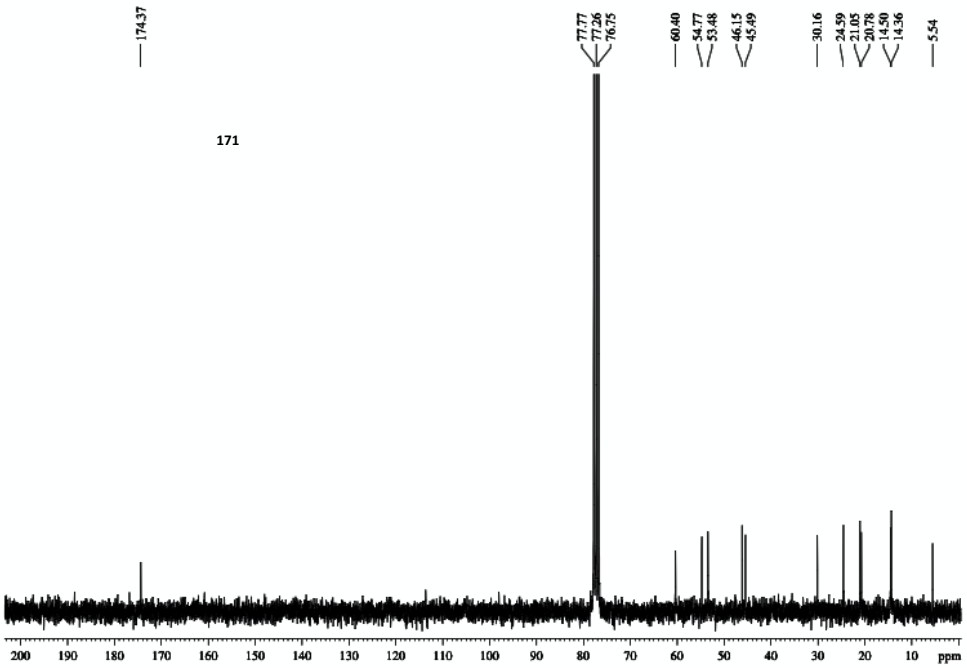
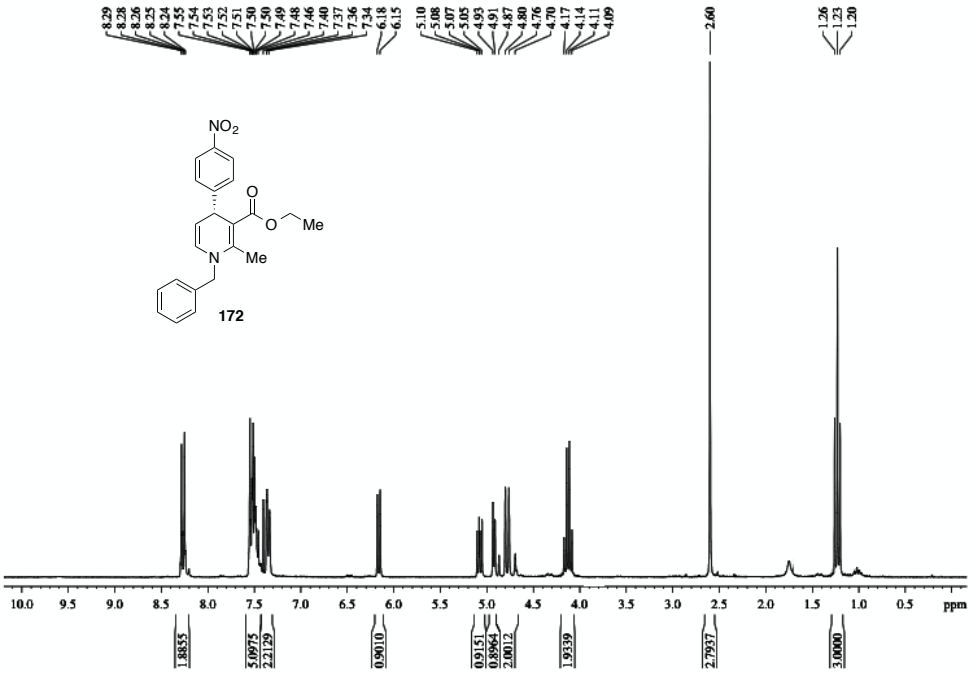
2.0000
0.7163
0.7083
2.9652
0.9504
2.2858
9.1962
6.3661


174.37
77.77
77.26
76.75
60.40
54.77
53.48
46.15
45.49
30.16
24.59
21.05
20.78
14.50
14.36
5.54
171
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.29
8.28
8.26
8.25
8.24
7.55
7.54
7.53
7.52
7.51
7.50
7.50
7.49
7.48
7.46
7.40
7.37
7.36
7.34
6.18
6.15
5.10
5.08
5.07
5.05
4.93
4.91
4.87
4.80
4.76
4.70
4.17
4.14
4.11
4.09
2.60
1.26
1.23
1.20
NO2
O
O
Me
N
Me
172
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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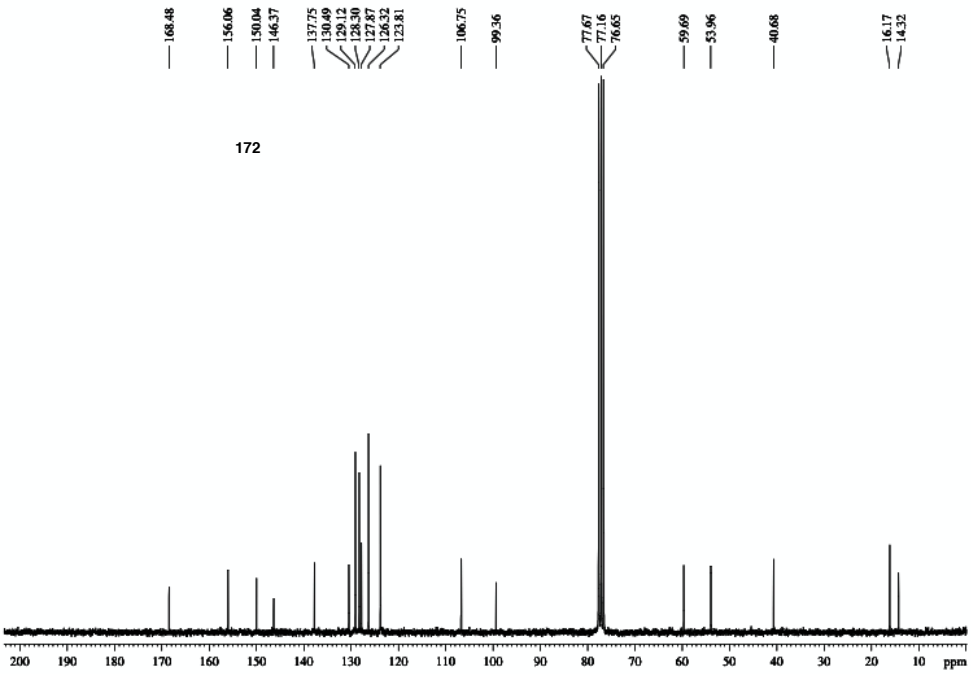
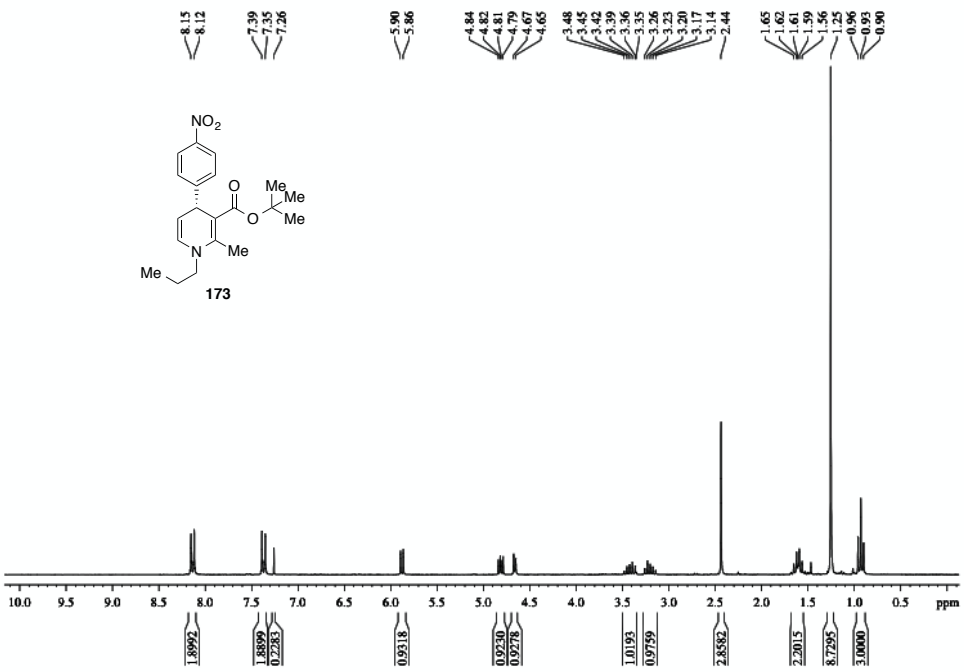
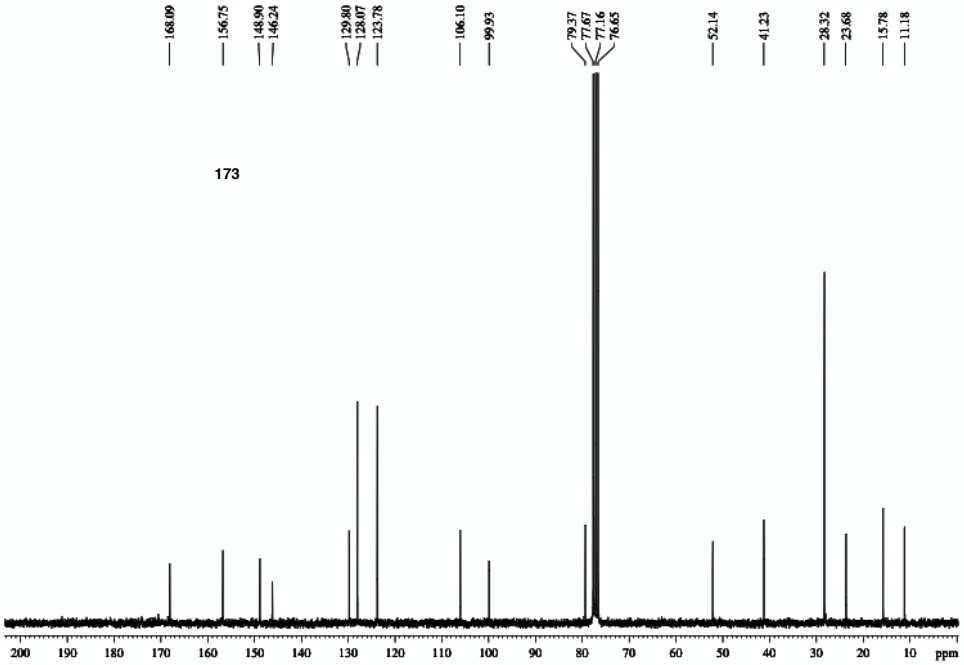
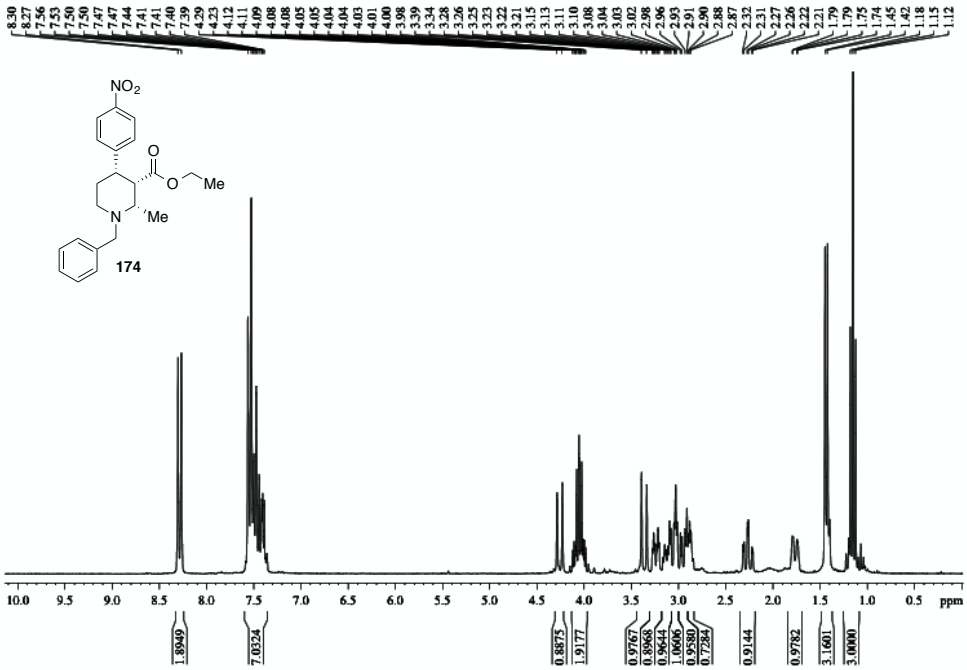
5.0975
2.2129
0.9010
0.9151
0.8964
2.0012
1.9339
2.7937
3.0000


168.48
156.06
150.04
146.37
137.75
130.49
129.12
128.30
127.87
126.32
123.81
106.75
99.36
77.67
77.16
76.65
59.69
53.96
40.68
16.17
14.32
172
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.15
8.12
7.39
7.35
7.26
5.90
5.86
4.84
4.82
4.81
4.79
4.67
4.65
3.48
3.45
3.42
3.39
3.36
3.35
3.26
3.23
3.20
3.17
3.14
2.44
1.65
1.62
1.61
1.59
1.56
1.25
0.96
0.93
0.90
NO2
O
Me
Me
O
Me
N
Me
Me
173
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.8992
1.8899
0.2283
0.9318
0.9250
0.9278
1.0193
0.9759
2.8582
2.2015
8.7295
3.0000


168.09
156.75
148.90
146.24
129.80
128.07
123.78
106.10
99.93
79.37
77.67
77.16
76.65
52.14
41.23
28.32
23.68
15.78
11.18
173
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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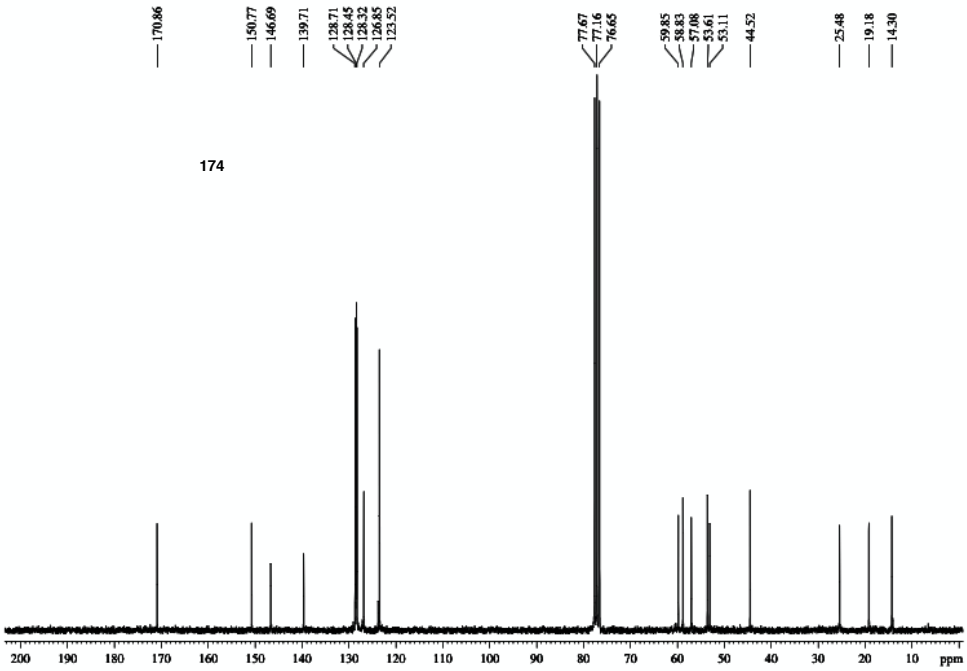
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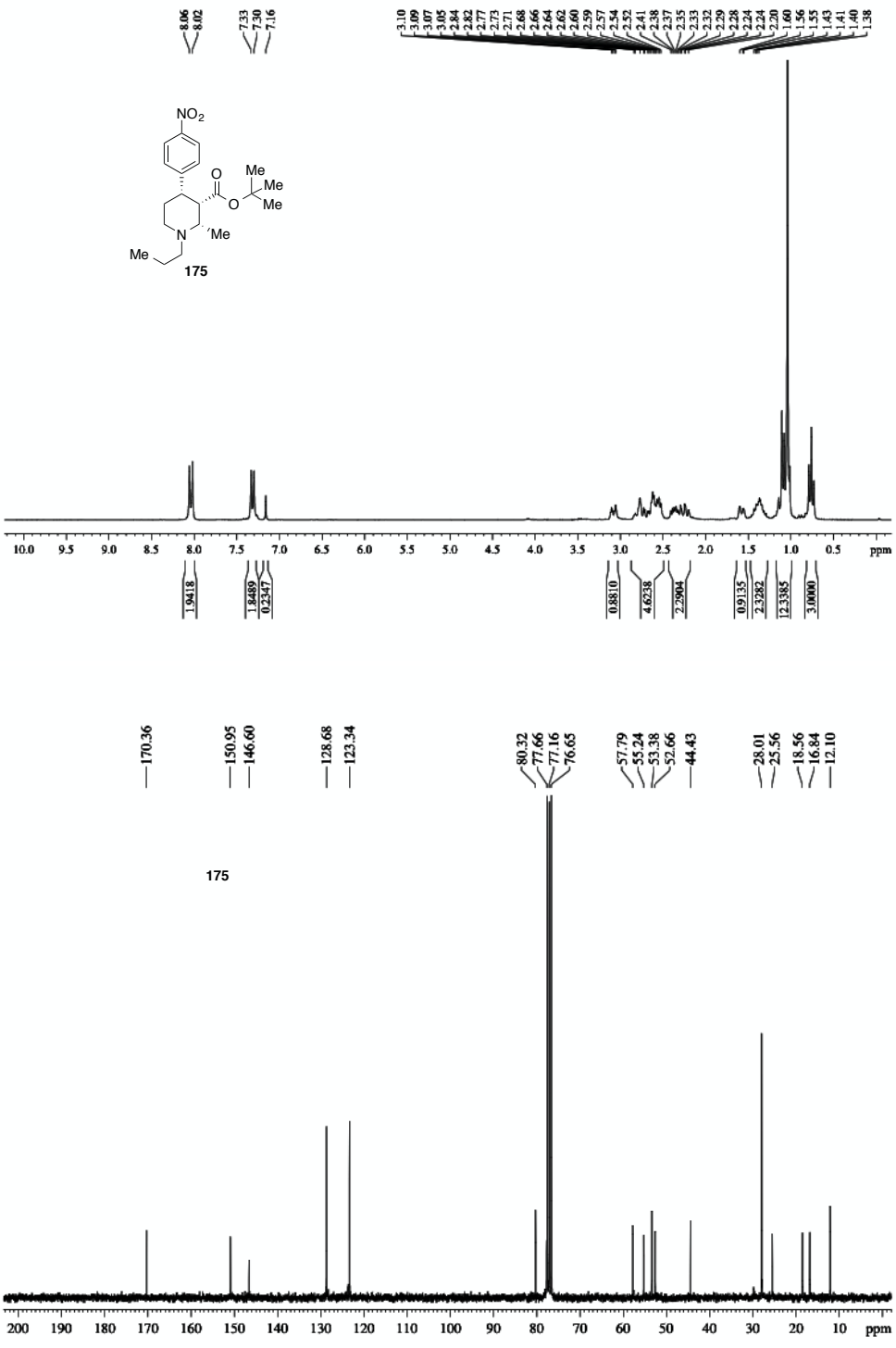
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1.56
1.55
1.43
1.41
1.40
1.38
NO2
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Me
O
N
Me
Me
175
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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1.8489
0.2347
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0.9135
2.3282
12.3385
3.0000
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77.16
76.65
57.79
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52.66
44.43
28.01
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175
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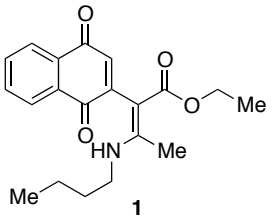
# Appendix 2: Summary of compound structures

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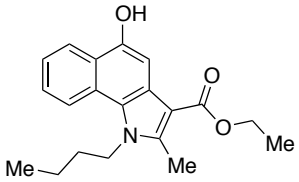


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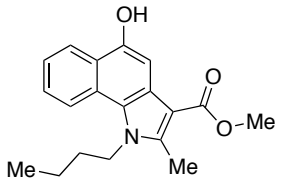


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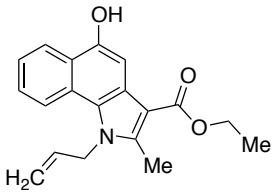


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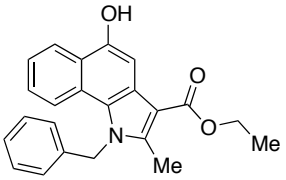


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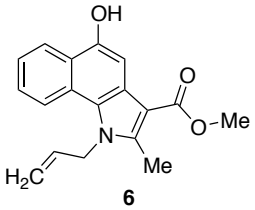


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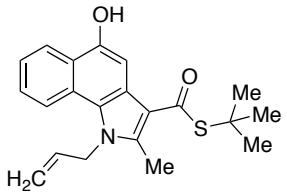


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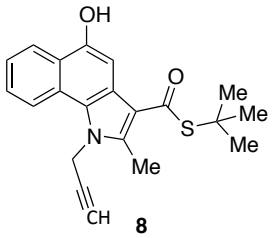


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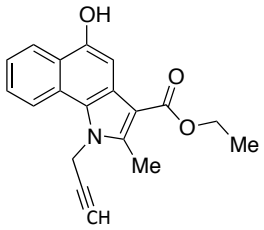


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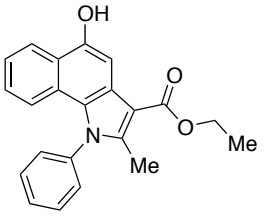


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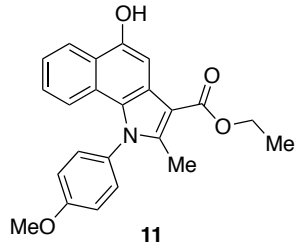


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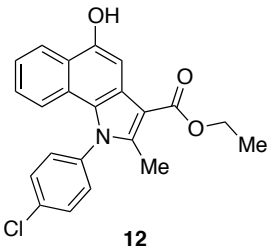


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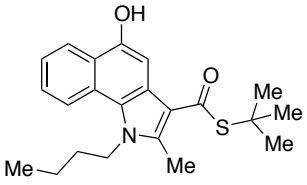


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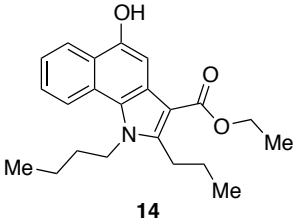


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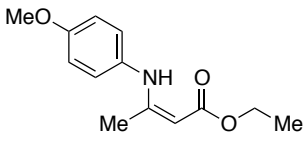


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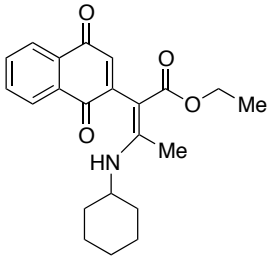


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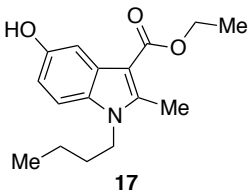


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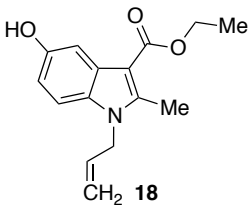


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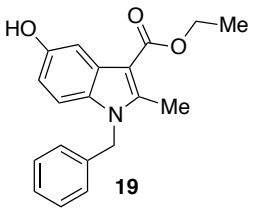
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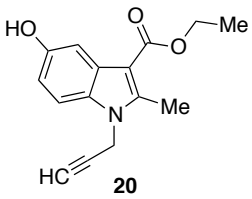
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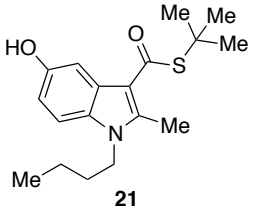
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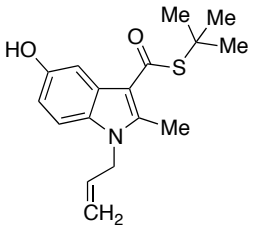
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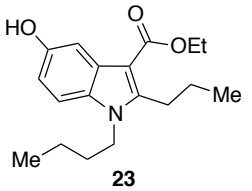
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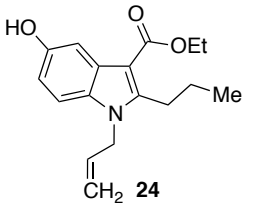
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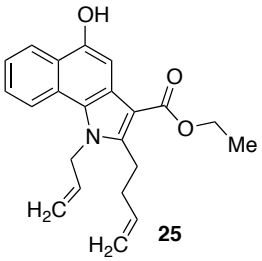
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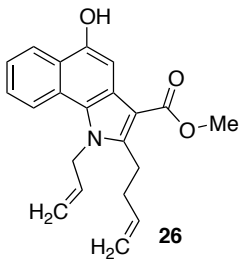
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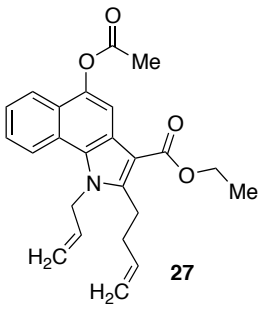
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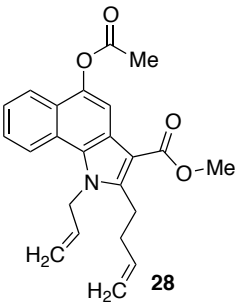
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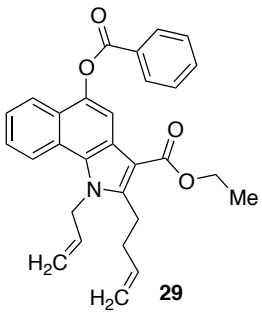
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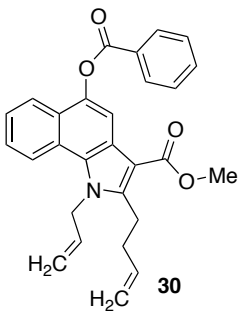
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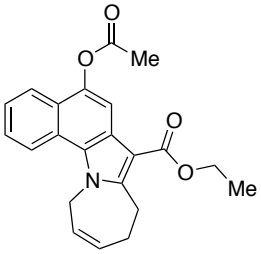
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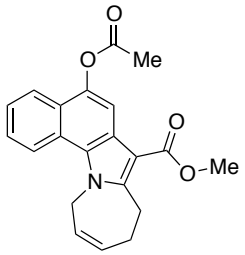
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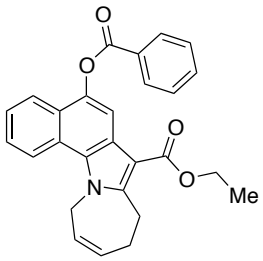
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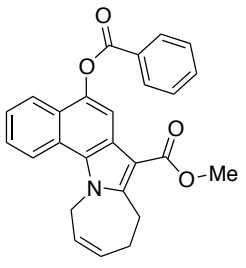

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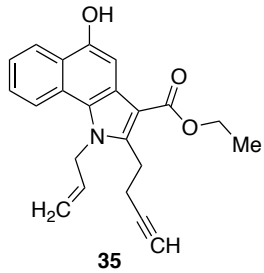

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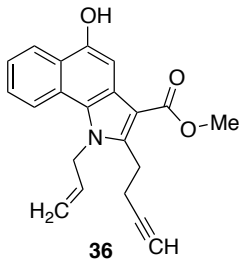

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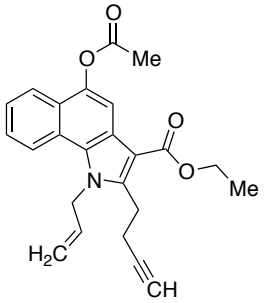

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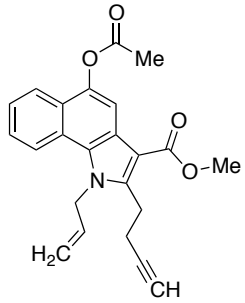

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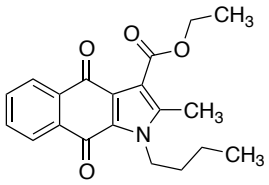

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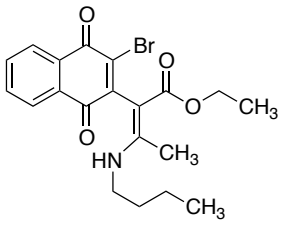

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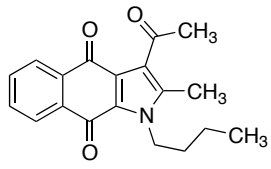

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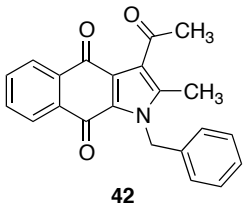

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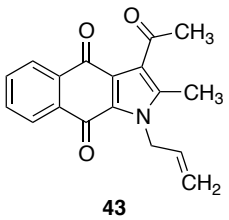

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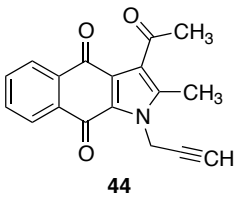

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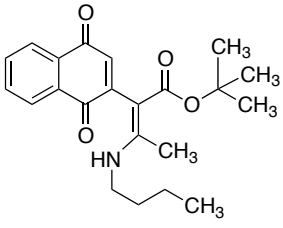

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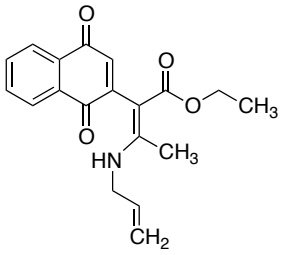

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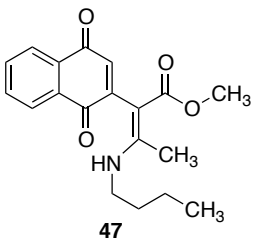

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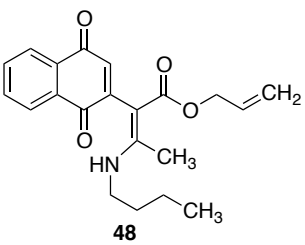

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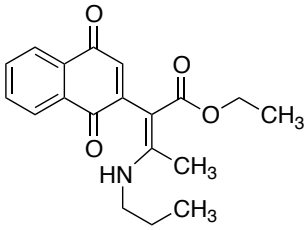

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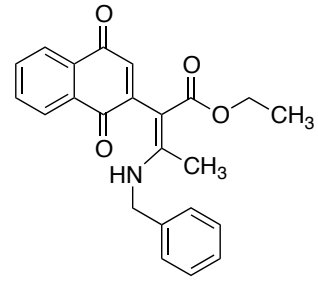

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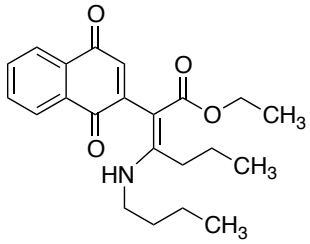

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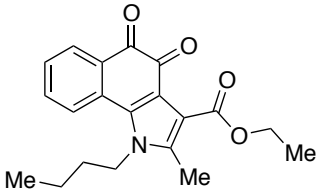

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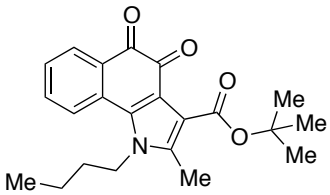

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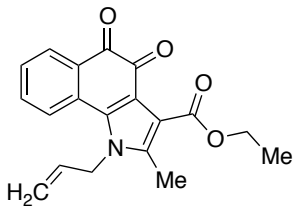

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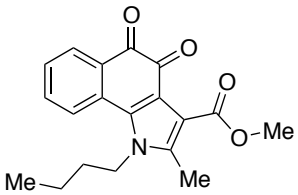

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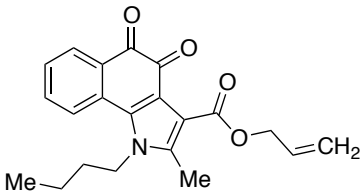

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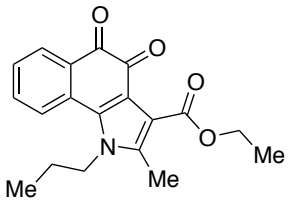

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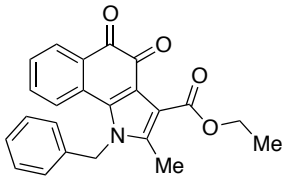

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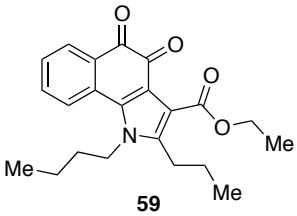

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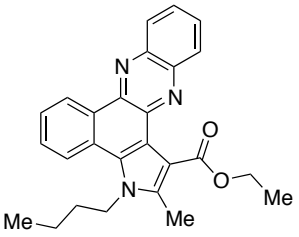

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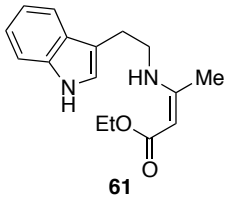

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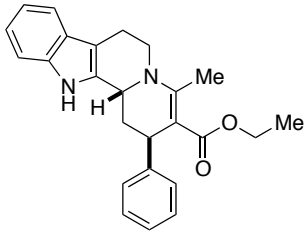

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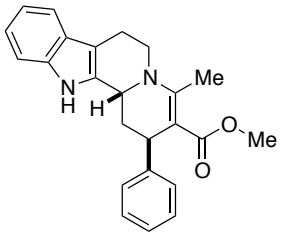

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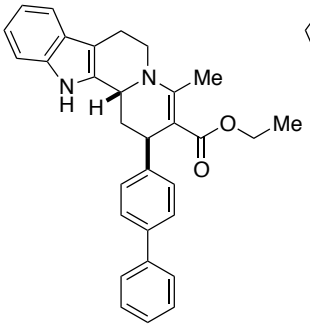

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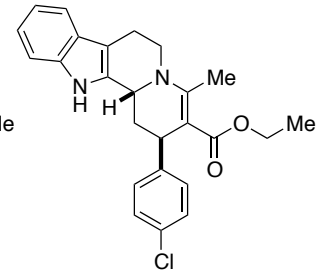

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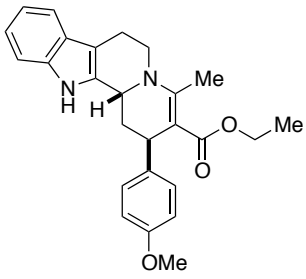

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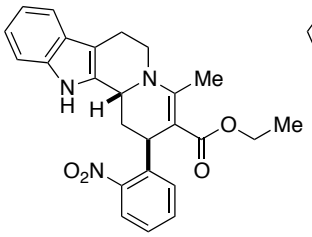

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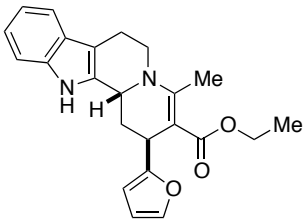

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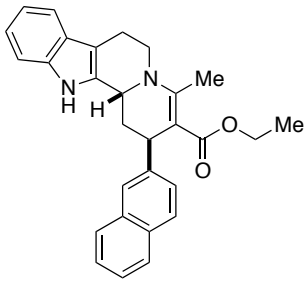

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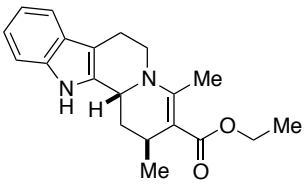

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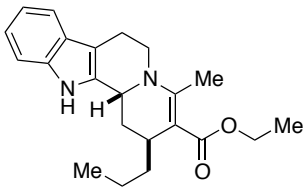

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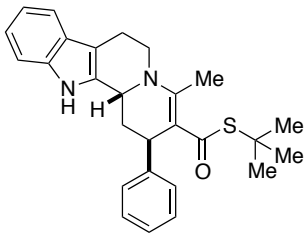

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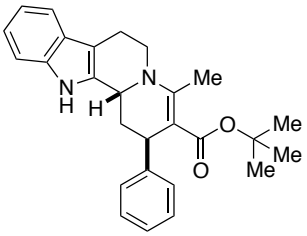

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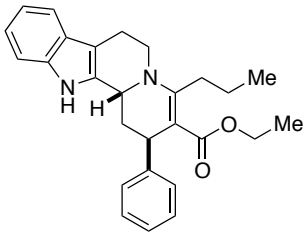

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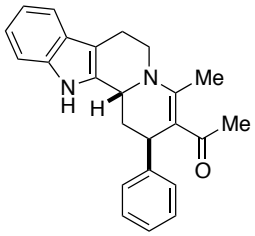

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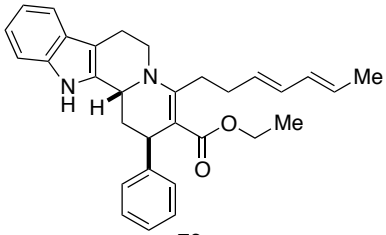

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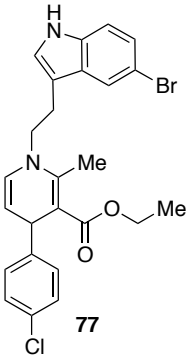

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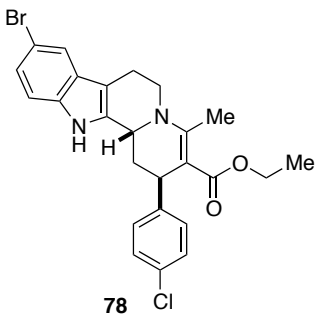

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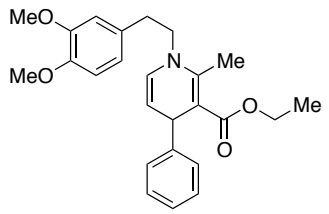


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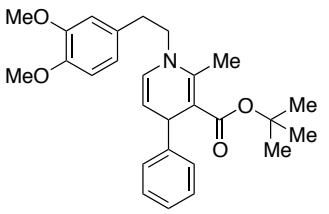


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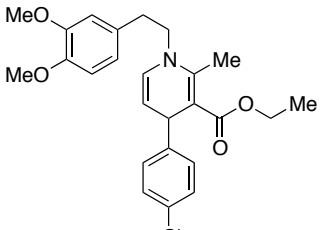


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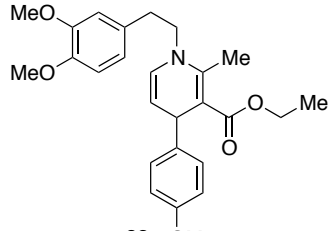


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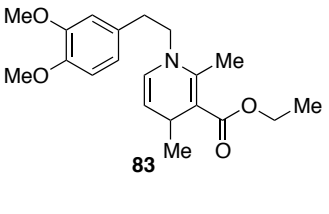


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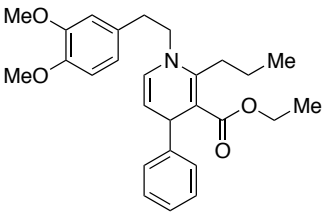


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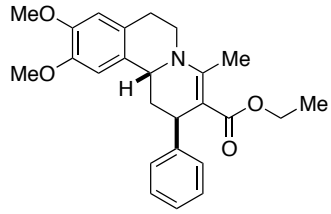


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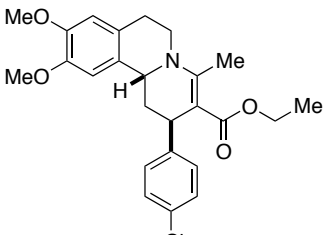


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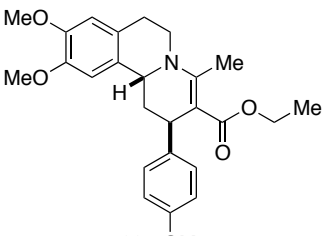


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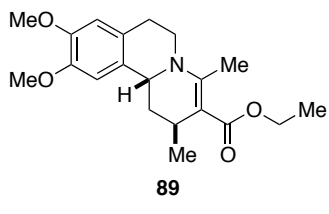


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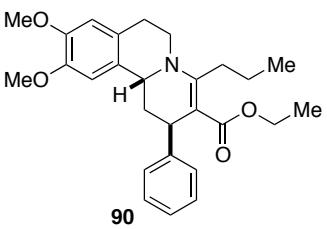


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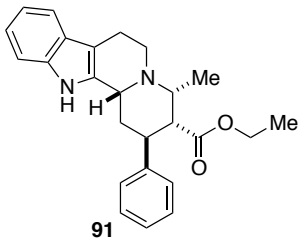


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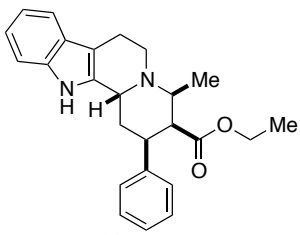


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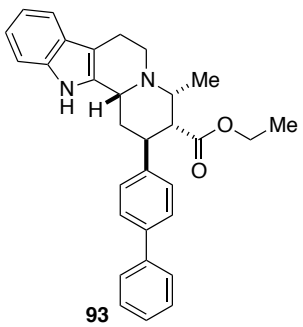


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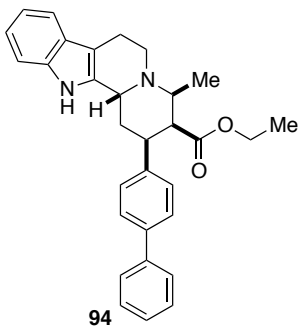


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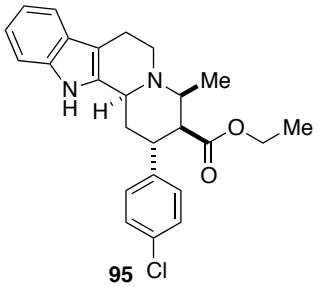

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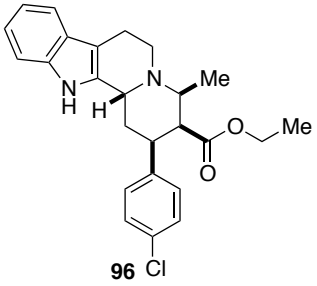

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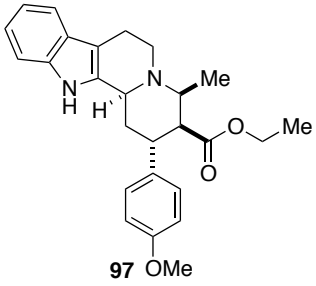

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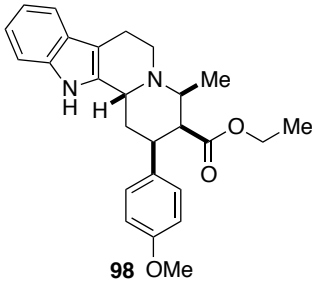

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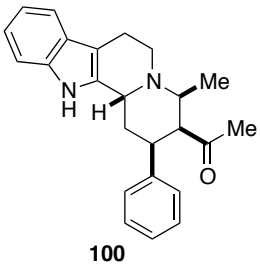

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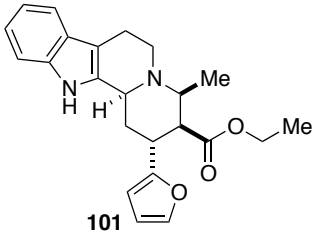

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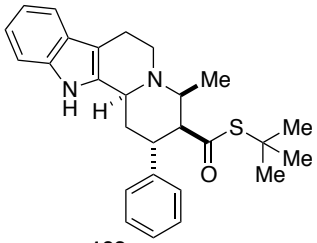

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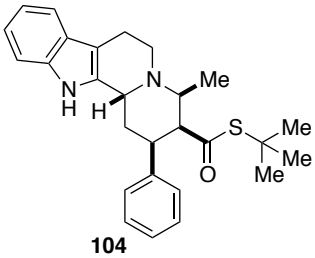

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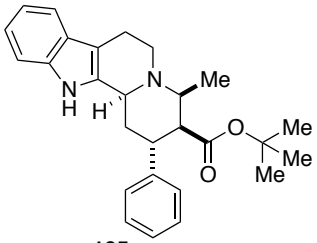

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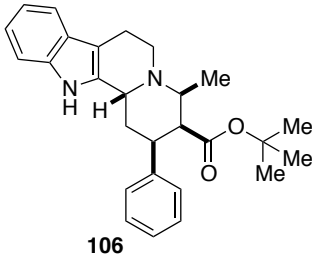

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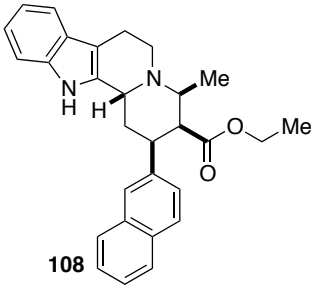

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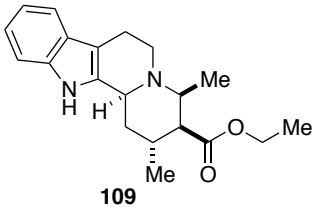

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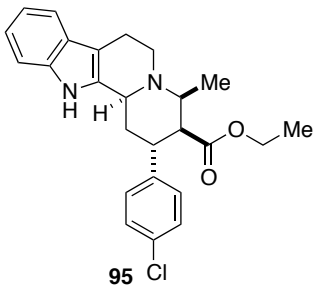

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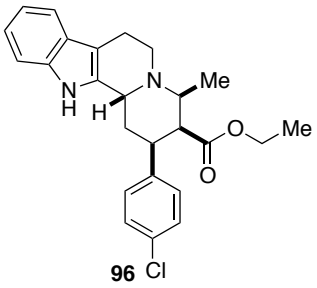

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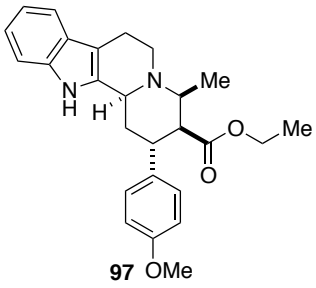

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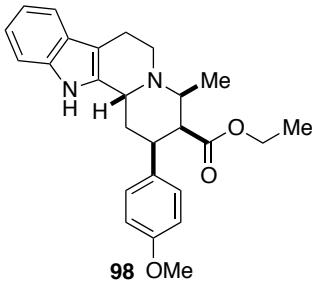

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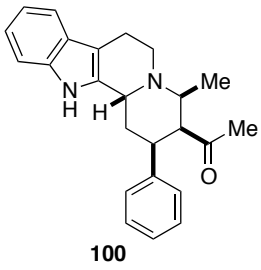

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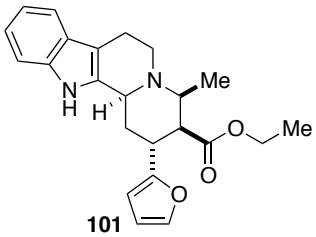

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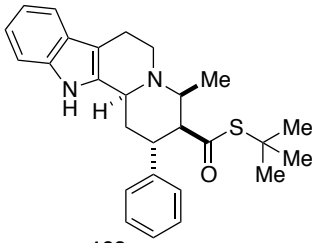

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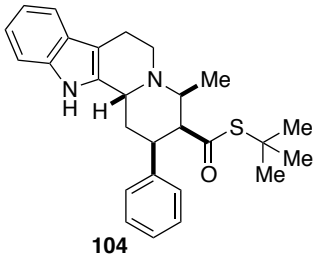

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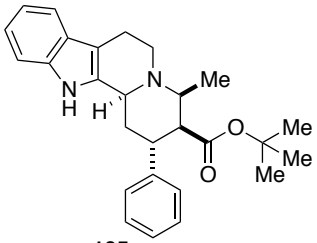

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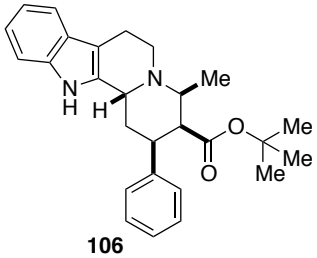

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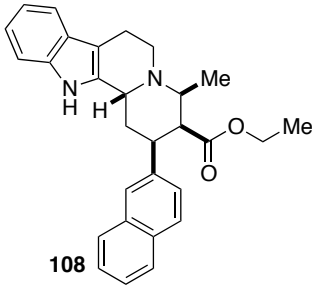

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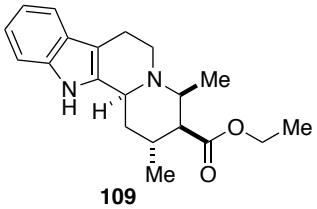

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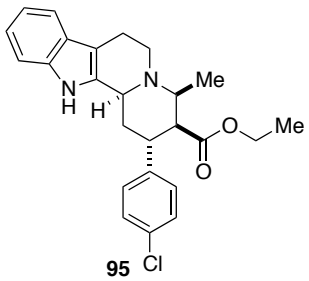


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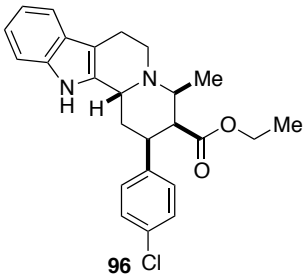


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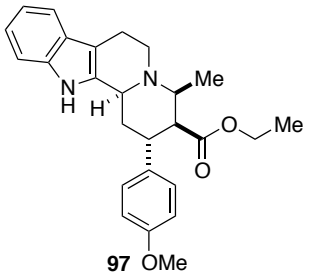


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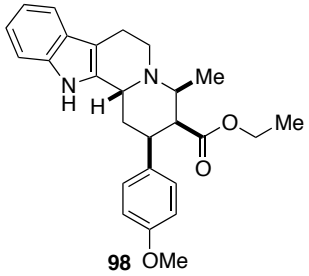


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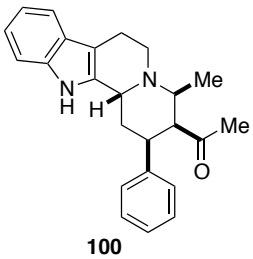


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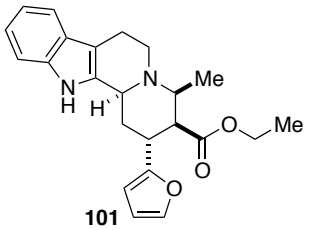


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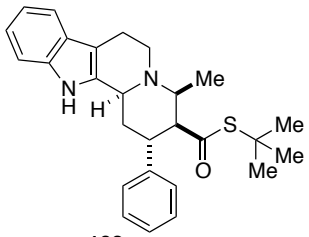


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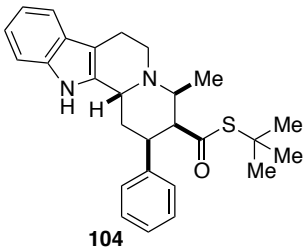


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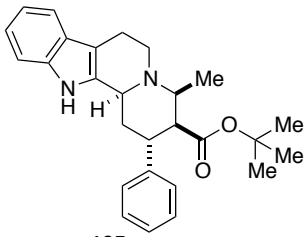


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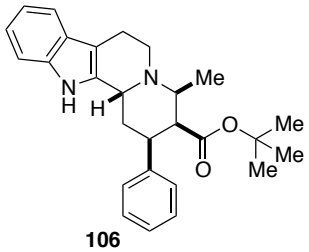


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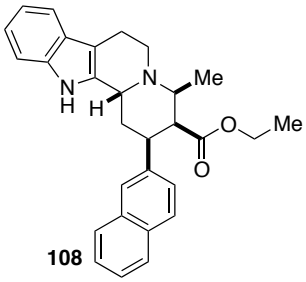


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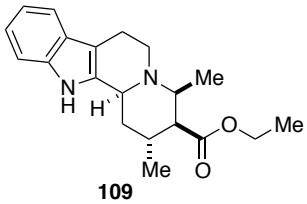


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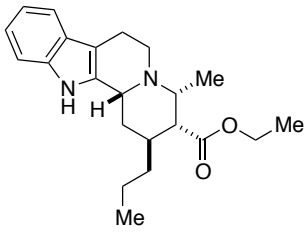


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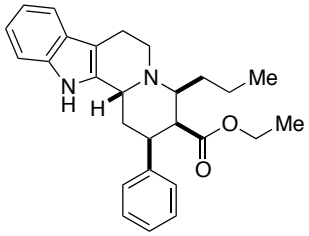


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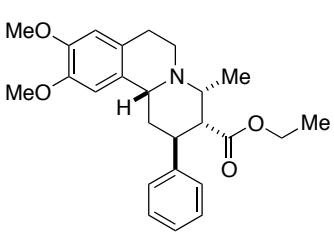


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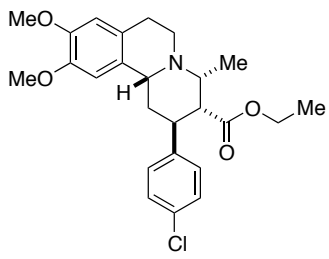


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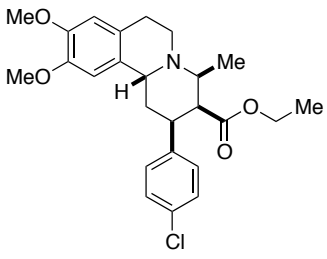


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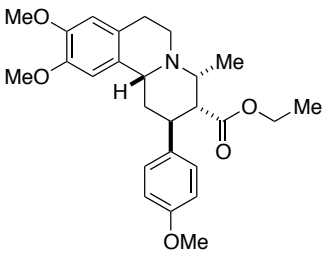


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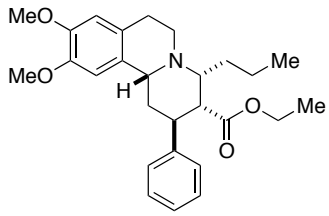


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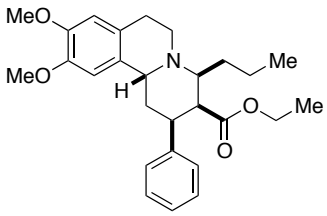


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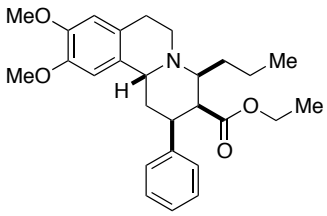


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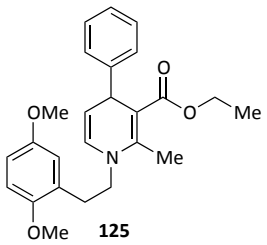


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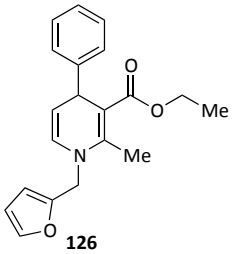


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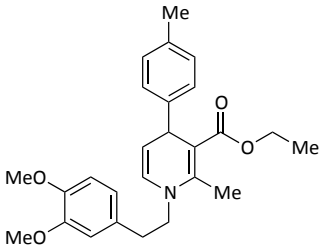


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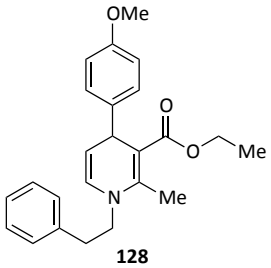


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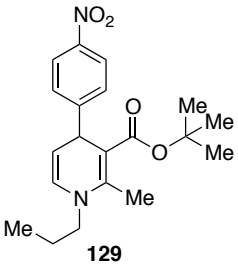


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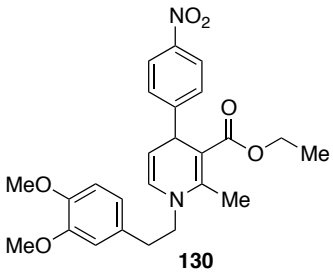


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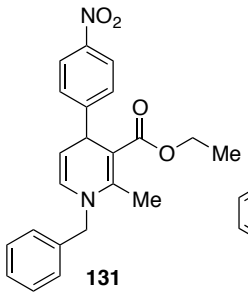


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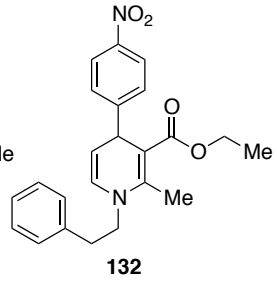


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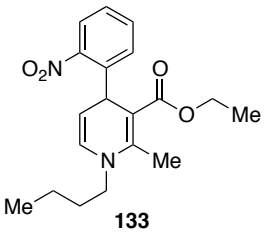


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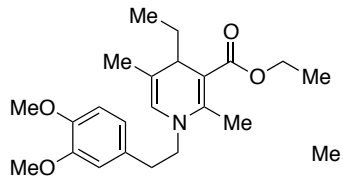

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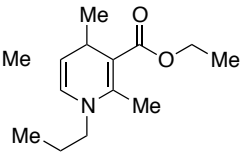

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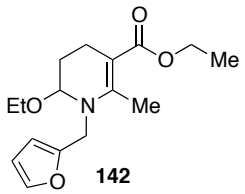

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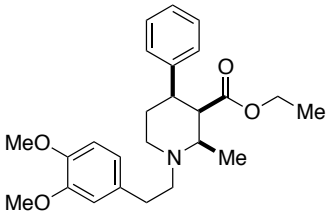

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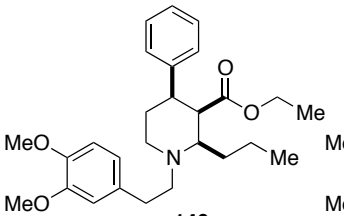

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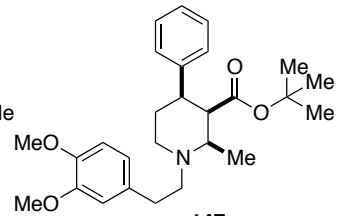

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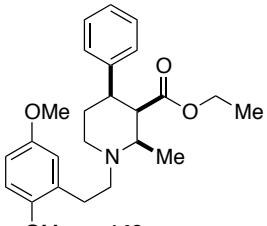

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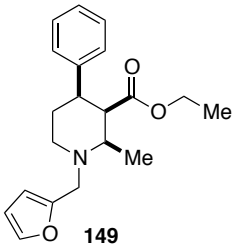

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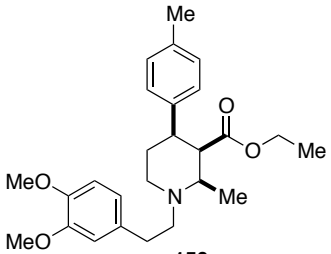

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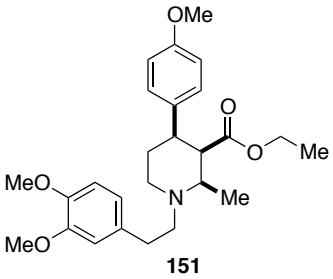

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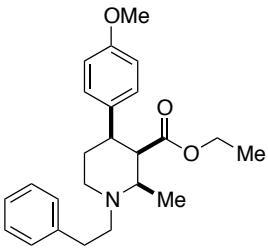

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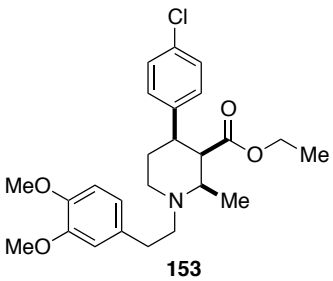

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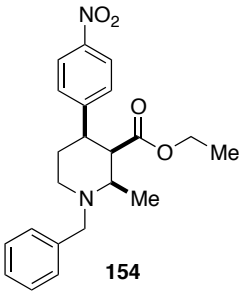

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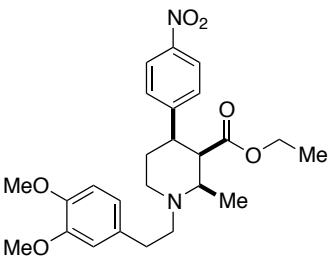

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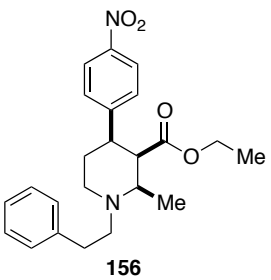

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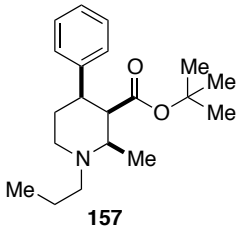

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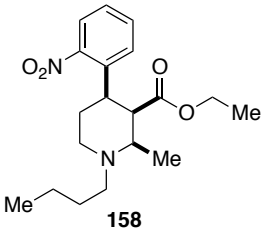

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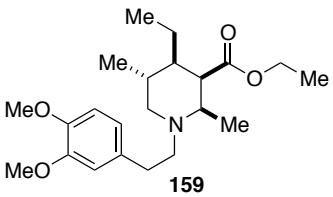

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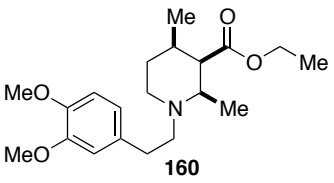
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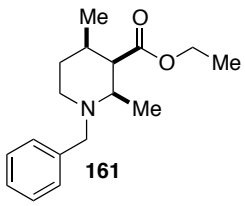
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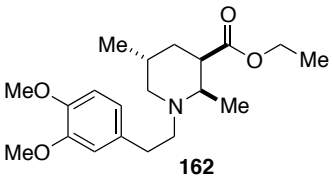
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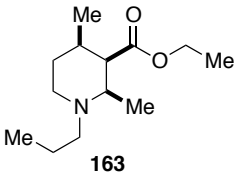
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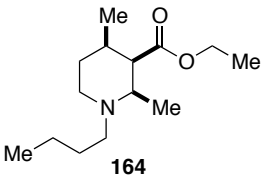
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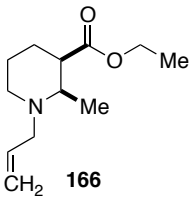
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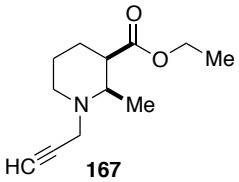
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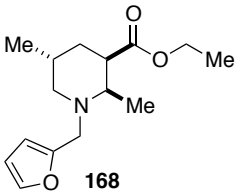
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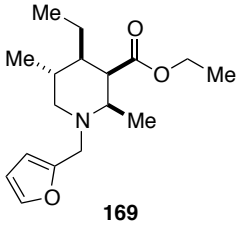
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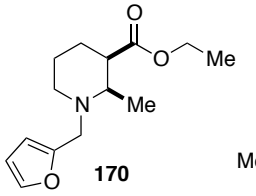
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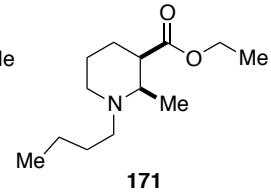
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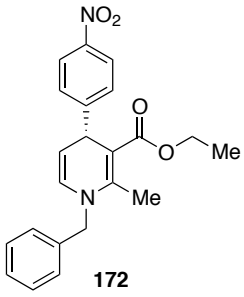
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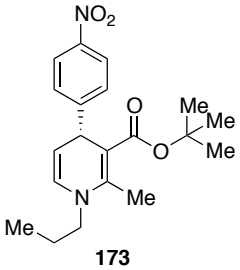
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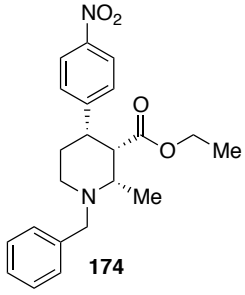
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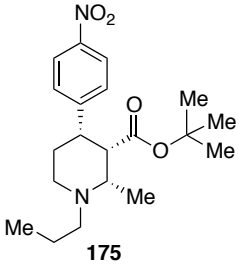
**175**

# Appendix 3: Publications